

[AM100226]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S) : PICKAR, J., DEY M.  
SERIAL NO. : 09/808,878  
FILED : March 15, 2001  
TITLE : HORMONE REPLACEMENT THERAPY  
ART UNIT : 1617  
EXAMINER : M. Bahar

Assistant Commissioner  
for Patents  
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132

SIR:

I, ROGERIO A. LOBO, M.D., declare as follows:

1. I am currently a Professor of Obstetrics & Gynecology at the Department of Obstetrics and Gynecology, Columbia University in New York, New York, and I served as Rappleye Professor and Chairman of the Department of Obstetrics and Gynecology from 1995 until July 2002. I received a medical degree from Georgetown University Medical School in 1974. I completed an internship from 1974 to 1975 and a residency from 1975 to 1978 at the University of Chicago, Department of Obstetrics & Gynecology. I was a Clinical Research Fellow at the University of Southern California Medical Center in Los Angeles, California from 1978 to 1980.

2. From 1978 until 1995, I held a number of academic medical positions at the University of Southern California, Los Angeles, California. From 1978 to 1980, I was a Clinical Instructor, Division of Reproductive Endocrinology and Infertility, Department of

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Obstetrics and Gynecology. I was an Assistant Professor, Department of Obstetrics & Gynecology from 1980 to 1984, an Associate Professor from 1984 to 1988, and a Professor from 1988 to 1995. From 1984 to 1995, I was Chief and Director of the Division of Reproductive Endocrinology and Infertility.

3. In the past twenty-three years, I have been an author or co-author of at least 313 papers published in peer-reviewed journals, 99 book chapters and 314 abstracts, and have been an editor of 25 books. Many of these publications are in the area of the menopause and treatments of the symptoms of menopause including hormone replacement therapy. (See, e.g., Rogerio A. Lobo, ed., Treatment of the Postmenopausal Woman: Basic and Clinical Aspects (2d ed., Philadelphia, PA: Lippincott Williams & Wilkins 1999)).

4. I am a member of a number of professional societies, including the International Menopause Society and the North American Menopause Society. I have served as a consultant to and have served on the editorial board of numerous medical journal specializing in obstetrics and gynecology, including *Obstetrics and Gynecology*, *The Journal of Reproductive Medicine* and *Fertility and Sterility*. Additional acts about my background and qualifications including a list of my publications are set forth in my curriculum vitae, attached as Exhibit A.

5. My private practice consists of gynecology with a focus on the treatment of premenopausal, menopausal and postmenopausal women. I have also participated in a number of clinical studies evaluating various treatments, including hormone replacement therapy, for the symptoms of menopause including hot flushes and decreased bone density.

6. By way of background, menopause generally refers to the cessation of the menses and ovarian function. In other words, the ovaries no longer produce estrogen. Approximately one-third of a woman's life is spent in the estrogen-deficient postmenopausal

state. Symptoms of estrogen deficiency include hot flashes, vaginal atrophy, depression, decrease in bone mass and changes in blood lipid levels, which may be precursors to cardiovascular diseases. Conjugated equine estrogens ("CEE") have been prescribed for over 50 years to treat these symptoms. However, for a woman with an intact uterus, estrogen therapy has been shown to increase the risk of endometrial hyperplasia (abnormalities in the cells that are a precursor to endometrial carcinoma) and endometrial carcinoma (endometrial cancer). The risk is substantially reduced when a progestin is administered concurrently.

7. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial demonstrated that estrogen-progestin combinations protect against endometrial hyperplasia. (See The Writing Group for the PEPI Trial, "Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial," JAMA 275(5):370-5 (1996)). The PEPI trial involved 596 healthy postmenopausal women aged 45 to 74 years at seven clinical centers in the U.S. from 1987 to 1993. The women were randomly assigned to one of five treatment groups: (1) a placebo; (2) 0.625 mg CEE daily; (3) 0.625 mg CEE daily plus 10 mg of a progestin, medroxyprogesterone acetate ("MPA") for 12 days per month; (4) 0.625 mg CEE daily plus 2.5 mg MPA daily<sup>1</sup>; or (5) 0.625 mg of estrogen daily plus 200 mg of a natural (micronized) progesterone for 12 days per month. A large proportion of women with a uterus who received unopposed 0.625 mg CEE developed endometrial hyperplasia. However, the addition of a progestin, 2.5 mg MPA, to the 0.625 mg CEE provided protection of the endometrium.

8. For the past 20 years, 0.625 mg CEE has been accepted as the standard dosage of estrogen necessary to relieve the symptoms of menopause, including hot flashes

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<sup>1</sup> This is the regimen used in PREMPRO, Wyeth's commercially-marketed combination low dose hormone replace therapy.

and bone loss. (See, e.g., Lindsay et al., Obstetrics and Gynecology, 63:759-763 (1984)).

The dosage of 2.5 mg of MPA has been recognized as the minimum amount needed to oppose 0.625 mg CEE and protect the endometrium. This combination of 0.625 mg CEE plus 2.5 mg MPA daily has been the most commonly prescribed hormone replacement therapy regimen in the United States. (See Archer et al., Fertility and Sterility, 75:1080-1087 (2001)).

9. A double blind clinical study of postmenopausal women was conducted using combinations of conjugated equine estrogens ("CEE") and the progestin, medroxyprogesterone acetate ("MPA"). Patients received continuous and uninterrupted treatment for 13 or 26 cycles. This study is referred to as the Women's Health, Osteoporosis, Progestin, Estrogen study ("H.O.P.E. study"). The study was conducted at 57 centers across the United States and included 2,673 healthy postmenopausal women aged 40 to 65. I worked with other scientists and doctors to develop the clinical protocol for the H.O.P.E. study and was involved as a trial investigator.

10. The objectives of the H.O.P.E. study were to evaluate the safety and efficacy of lower doses of Premarin and MPA in reducing the incidence of endometrial hyperplasia, relieving menopausal symptoms and maintaining an acceptable metabolic profile. Another sub-part of the study focused on bone mineral density and was conducted over a 26 cycle period.

11. The doses used in the H.O.P.E. study consisted of eight regimens administered daily: (1) 0.625 mg CEE; (2) 0.45 mg CEE; (3) 0.3 mg CEE; (4) 0.625 mg CEE plus 2.5 mg MPA ("PREMPRO"); (5) 0.45 mg CEE plus 2.5 mg MPA; (6) 0.45 mg CEE plus 1.5 mg MPA; (7) 0.3 mg CEE plus 1.5 mg MPA; and (8) a placebo.

12. It was conventional wisdom that the dose of 0.625 mg CEE was the minimum effective dose to relieve vasomotor symptoms ("hot flashes"). I and others



expected that the study would show that there would be a dose response such that the lower combination doses of CEE and MPA would have some effect in reducing the number and severity of hot flushes compared with the placebo, but far less of an effect than the standard dose of CEE 0.625 plus 2.5 mg MPA. In fact, I and others were interested in seeing the results of the various lower doses, but doubted the study was worth the economic effort.

13. Relief of vasomotor symptoms was analyzed in patients who experienced at least an average of 7 to 8 moderate-to-severe hot flushes per day during the 7-day period just prior to the initiation of treatment in this study.

14. It was very surprising and unexpected that the data from the H.O.P.E. study demonstrated that all doses of CEE and MPA reduced the number and severity of hot flushes experienced by the women in this study compared with women taking placebo. It was unexpected that providing a daily dosage of 1.5 mg MPA in combination with the lower doses, 0.45 or 0.30 mg, CEE, rapidly reduced the number and severity of hot flushes to the same extent as the much higher and commercially available dose combination containing 0.625 mg CEE and 2.5 mg MPA.

15. Moreover, at these particular low doses of 1.5 mg MPA, an additive effect of vasomotor symptom relief is seen. The H.O.P.E. study demonstrated that dosages of CEE and MPA may be better than equivalent dosages of unopposed CEE for vasomotor symptom relief. Previous studies with various dosages of CEE showed no additive effect of MPA on vasomotor relief. (See Greendale et al., Obstetrics and Gynecology, 92:982-988 (1998)). Instead, the presence of MPA was thought to be merely prophylactic (to prevent endometrial cancer). The H.O.P.E. study surprisingly demonstrated that at these low doses MPA may contribute to ameliorating the vasomotor symptoms.

16. Prior to the H.O.P.E. study, the dosage of MPA necessary to provide endometrial protection with lower dosages of CEE was unknown. We entered uncharted waters in conducting the H.O.P.E. study as to the endometrial risk posed by the lower daily dosage combinations of 0.45 or 0.3 mg CEE and 1.5 mg MPA. The endometrial biopsies<sup>2</sup> evaluated as part of the H.O.P.E. study demonstrated that providing a daily dosage of 1.5 mg MPA effectively inhibited the development of endometrial hyperplasia when opposing the lower doses, 0.45 or 0.30 mg, CEE. These biopsy results were not statistically different from the higher dose hormone replacement therapy combination containing 2.5 mg MPA.

17. The prior art Plunkett patent cited by the examiner is directed to combinations of various estrogens and progestins. Plunkett lists a myriad of such combinations over a variety of dosage ranges, in both cyclic and continuous regimes. There is nothing in the Plunkett patent that teaches one skilled in the art to select the combination of 1.5 mg MPA and about 0.3 to about 0.45 mg CEE for relief of vasomotor symptoms of menopause from the thousands of possible estrogen-progestin combinations.

18. The preferred dosages of MPA and CEE that Plunkett discloses are 2.5 mg MPA and 0.600 mg CEE. These dosages are much higher than the dosages claimed in the present invention -- 1.5 mg MPA and about 0.3 to about 0.45 mg CEE.

19. Plunkett does not teach the importance of balancing the dosages of MPA and CEE, particularly at very low doses. Specifically, Plunkett does not teach that the selection of 1.5 mg MPA would provide relief of vasomotor symptoms achieved in combination with about 0.3 to about 0.45 mg CEE

20. Further, Plunkett does not teach that an additive vasomotor effect is exhibited by the low dose of MPA to the lower doses of CEE (0.3 to about 0.45 mg CEE).

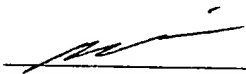
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<sup>2</sup> An endometrial biopsy is a cell sample of the endometrium taken to evaluate whether any abnormal cells exist.

21. In conclusion, the results of the H.O.P.E. study unexpectedly demonstrated that the combinations of a daily dosage of 1.5 mg MPA with 0.3 or 0.45 mg CEE are effective in treating vasomotor symptoms. In my opinion, these dosage combinations would not have been obvious at the time of the invention to relieve vasomotor symptoms.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the patent or any reexamination certificate issued therefor.

Dated: 4/1/03

  
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ROGERIO A. LOBO, M.D.

*Updated: 3/24/03*

## **Curriculum Vitae**

**ROGERIO A. LOBO, M.D.**

*Date of birth:* October 26, 1949

*Place of birth:* Hong Kong

*Citizenship:* Naturalized United States Citizen

*Marital Status:* Married (Jessie C. Lobo)

*Children:* Margaret J. Lobo  
Roger R. Lobo

*Social Security No.:* 579-72-6816

*Home Address and Telephone No.:* 31 Kent Road  
Scarsdale, New York 10583  
(914) 723-8925

*Business Address and Telephone No.* Columbia-Presbyterian Medical Center  
Department of Obstetrics & Gynecology  
622 West 168<sup>th</sup> Street  
New York, NY 10032  
(212) 305-2377

*Licensure and Certifications:* State of California Medical License  
No. G-36128

The University of the State of New York Medical License  
No. 198859

DEA No. AL822046

Diplomate, National Board of Medical Examiners, 1975

Diplomate, The American Board of  
Obstetrics and Gynecology, Inc. 1981

Diplomate, The American Board  
of Obstetrics and Gynecology, Inc.  
Division of Reproductive Endocrinology, 1982

Recertified Diplomate, The American  
Board of Obstetrics and Gynecology Inc. 1994

***Education:***

1967-1995

Georgetown University  
Washington, D.C.

B.Sc. (Cum Laude)  
Major: Biology

1970- 1974

Georgetown University Medical School  
Washington, D.C.  
M.D.

***Postgraduate Training:***

1974- 1975

Intern  
Department of Obstetrics & Gynecology  
The Chicago Lying-In-Hospital  
The University of Chicago  
Chicago, Illinois

1975- 1978

Resident  
Department of Obstetrics and Gynecology  
The Chicago Lying-In-Hospital  
The University of Chicago  
Chicago, Illinois

1978-1980

Infertility

Clinical Research Fellow  
Division of Reproductive Endocrinology and

Department of Obstetrics and Gynecology  
Los Angeles County/University of Southern  
California Medical Center  
Los Angeles, California

***Academic Positions:***

1978-1980

Clinical Instructor  
Division of Reproductive Endocrinology and Infertility  
Department of Obstetrics and Gynecology  
University of Southern California  
Los Angeles, California

1980-1984

Assistant Professor  
Department of Obstetrics and Gynecology  
University of Southern California  
Los Angeles, California

1984-1988

Associate Professor  
Department of Obstetrics & Gynecology  
University of Southern California  
Los Angeles, California

1988- 1985	Professor Department of Obstetrics & Gynecology University of Southern California Los Angeles, California
1984- 1995	Chief, Division of Reproductive Endocrinology and Infertility Department of Obstetrics and Gynecology Los Angeles County/University of Southern California Medical Center Los Angeles, California
1984-1995	Director, Reproductive Endocrinology and Infertility Training Program Fellows and students directed in training are underlined under list of publications
1995-2002	Rappleye Professor and Chairman Department of Obstetrics and Gynecology Columbia University College of Physicians and Surgeons New York, New York
7/1/02-present	Professor of Obstetrics & Gynecology Department of Obstetrics and Gynecology Columbia University College of Physicians and Surgeons New York, New York
<b><i>Other Hospital Affiliations:</i></b>	
1980- 1995	Consultant City of Hope National Medical Center Duarte, California
1984-1995	California Medical Center Los Angeles, California
1986-1991	Director University of Southern California/ California Hospital Reproductive Health Institute Los Angeles, California
1991- 1995	USC University Hospital Los Angeles, California

***Outside Consultantships:***

Abbott Diagnostics  
North Chicago, Illinois

Medical Advisory Board  
Mead Johnson Laboratories  
Princeton, New Jersey

Progynon Associates  
Rosemont, Illinois

Division of Endocrinology and Metabolism  
Robert Wood Johnson Pharmaceutical Research Institute  
New Brunswick, New Jersey

Advisory Board on Hormone Replacement Therapy  
Schering Laboratories  
Kenilworth, New Jersey

Reproductive Endocrinology Luminary Program  
Serono Laboratories  
Norwell, Massachusetts

Advisory Board  
TAP Pharmaceuticals, Inc.  
Deerfield, Illinois

Wyeth-Ayerst Research  
Philadelphia, Pennsylvania

Board of Trustees  
The Berlex Foundation  
Dumont, New Jersey

Advisory Boards:  
Solvay  
Ortho  
Lilly  
Merck

***Membership in Professional Societies:***

International Menopause Society  
Pacific Coast Fertility Society  
Society for Gynecologic Investigation  
The American College of Obstetricians and Gynecologists  
American Society for Reproductive Medicine  
The American Gynecological and Obstetrical Society  
The Endocrine Society  
The North American Menopause Society

***Membership in Committees:***

The Society of Reproductive Endocrinologists

1983- 1984	Medical Education Committee III-year students
1984-1985	Grand Rounds Program Coordinator Department of Obstetrics and Gynecology Los Angeles County/University of Southern California Medical Center Los Angeles, California
1984- 1987	Board of Directors Pacific Coast Fertility Society Los Angeles, California
1984	Awards Committee Pacific Coast Fertility Society Los Angeles, California
1984	Special Study Section National Institutes of Health Bethesda, Maryland
1984- 1995	Executive Committee Department of Obstetrics and Gynecology Los Angeles County/University of Southern California Medical Center, Los Angeles, California
1985- 1986	Search Committee for Dean University of Southern California School of Medicine Los Angeles, California
1985- 1995	Admissions Committee for Students University of Southern California School of Medicine Los Angeles, California
1986	External Referee Medical Research Council of Canada Ottawa, Canada
1986- 1995	Advisory Committee on Policy American Journal of Obstetrics & Gynecology
1987	Program Chairman Pacific Coast Fertility Society Los Angeles, California



1987- 1995	Ad Hoc Committee for Promotions University of Southern California School of Medicine Los Angeles, California
1987- present	Examiner Basic Obstetrics and Gynecology and Reproductive Endocrinology Oral Examinations The American Board of Obstetrics and Gynecology, Inc. Seattle, Washington
1988	Steering Committee National Cholesterol Education Program National Heart, Lung and Blood Institute National Institutes of Health Bethesda, Maryland
1988	Program Chairman Society for Gynecologic Investigation Washington, D.C.
1988	Chairman Poster Prize Presentation Committee The American Fertility Society Birmingham, Alabama
1988-1995	Chairman, Institutional Review Committee California Medical Center Los Angeles, California
1988-1995	Advisory Committee General Clinical Research Center University of Southern California School of Medicine Los Angeles, California
1988-1992	Reproductive Endocrinology Study Section Division of Research Grants National Institutes of Health Bethesda, Maryland
1989- 1995	Secretary-Treasurer Society for Gynecologic Investigation Washington, D.C.
1989	Exhibits Chairman Pacific Coast Fertility Society

1991- 1992	Los Angeles, California Vice President Pacific Coast Fertility Society La Mirada, California
1992- 1993	President Pacific Coast Fertility Society La Mirada, California
1992- 1996	Reviewers Reserve National Institutes of Health Bethesda, Maryland
1992- 1993	Program Chairman The North American Menopause Society Cleveland, Ohio
1993- 1996	Board of Directors The American Fertility Society Birmingham, Alabama
1995-	American Board of Obstetrics & Gynecology Division of Reproductive Endocrinology
1997-1998	President, Society for Gynecologic Investigation

***Committees at Columbia University  
College of Physicians and Surgeons:***

CPPN Board  
Executive Committee, Medical Board  
Surgical Directors Committee  
Clinical Chairs Committee  
Directors of Service Committee  
Dean's Committee on Hospital Appointments

***Consultant for the Following Journals:***

Acta Endocrinologica  
American Journal of Medicine  
American Journal of Nephrology  
Archives of Internal Medicine  
Clinical Chemistry  
Contraception  
Endocrinology  
Epidemiology  
European Journal of Obstetrics,  
Gynecology and Reproductive Biology  
Fertility and Sterility  
Gynecologic Oncology  
Gynecological Endocrinology  
International Journal of Gynaecology and Obstetrics

Journal of Endocrinological Investigation  
Journal of the American Medical Association  
Life Sciences  
New England Journal of Medicine  
Obstetrics and Gynecology  
The Journal of Clinical Endocrinology  
and Metabolism  
The Journal of Reproductive Medicine  
Journal of In Vitro Fertilization and Embryo Transfer  
Proceedings of the National Academy of Science  
Australian Medical Journal

***Editorship:***

Editor-in-Chief  
Journal of Society for Gynecological Investigation

***Journal Editorships/Editorial Board:***

Clinical Pathological Conferences in  
Obstetrics and Gynecology

Clinics in Endocrinology and Metabolism

Fertility and Sterility  
(Editorial Board, 1986-1993)

Gynecological Endocrinology  
(Editorial Board)

Journal of the Society for Gynecologic  
Investigation

Menopause Management  
(Editorial Board)  
Seminars in Reproductive Endocrinology

The American Journal of Obstetrics and  
Gynecology, Society for Gynecologic  
Investigation issue (1986-1993)

The Journal of Maternal-Fetal Medicine  
(Editorial Board)

The Journal of Reproductive Medicine  
(Editorial Board)

The Journal of Clinical Endocrinology & Metabolism  
(Editorial Board) (1/1/97-12/31/2000)

Contemporary Clinical Gynecology & Obstetrics

***Lectureships:***

(Editorial Board) 8/1/2000-

Multiple visiting professorships and speaking engagements. Postgraduate courses and other teaching assignments (medical students, residents, etc) not specifically listed.

***Honors and Awards:***

Serono Award (In-Training) Paper entitled: The Role of DHEA-S in the Evaluation of Hirsute Women. Presented at the 27th Annual Meeting of the Pacific Coast Fertility Society, October 17-21, 1979, Rancho Mirage, California.

Serono Award (In-Training). Paper entitled: Elevations in Unbound Serum Estradiol as a Possible Mechanism for Inappropriate Gonadotropin Secretion in Women with PCO Presented at the 28th Annual Meeting of the Pacific Coast Fertility Society, October 15-19, 1980, Scottsdale, Arizona.

Wyeth Award. Paper entitled: The Relationship Between Psychological Stress, Neurotransmitters and Androgen Secretion in Women With PCO. Presented at the 29th Annual Meeting of the Pacific Coast Fertility Society October 14-18, 1981, Rancho Mirage, California

Squibb Award. Paper entitled: Hirsutism in Polycystic Ovary Syndrome (PCO). Presented at the 30th Annual Meeting of the Pacific Coast Fertility Society, October 13-17, 1982, Scottsdale, Arizona

Squibb Award  
Paper entitled: The Effects of Spironolactone on Adrenal Steroidogenesis in Hirsute Women  
Presented at the 32nd Annual Meeting of the Pacific Coast Fertility Society  
September 19-23, 1984, Rancho Mirage, California

Wyeth Award  
Paper entitled: Prolactin (PRL) Modulates Peripheral Androgen Metabolism (PAM)  
Presented at the 33rd Annual Meeting of the

Pacific Coast Fertility Society  
April 24-28, 1985  
Las Vegas, Nevada

**Wyeth Award**

Paper entitled: Acute Modulation of the  
Hypothalamic-Pituitary Axis (HPA) by  
Testosterone (T) in Normal Women  
Presented at the 32nd Annual Meeting of the Society for  
Gynecologic Investigation  
March 20-23, 1985  
Phoenix, Arizona

**Lester T. Hibbard Award**

Outstanding Faculty, 1985  
Department of Obstetrics and Gynecology  
Los Angeles County/University of Southern  
California Medical Center  
Los Angeles, California

**Second Prize**

Paper entitled: Genital Skin  $5\alpha$ Reductase  
Activity ( $5\alpha$ RA): A Marker of Androgenicity  
in Women  
Presented at the 4th Annual Meeting of  
The American Gynecological and Obstetrical Society  
September 4-7, 1985  
Hot Springs, Virginia

**Squibb Award**

Paper entitled: Clinical Heterogeneity in  
Turner's Syndrome  
Presented at the 34th Annual Meeting of the  
Pacific Coast Fertility Society  
April 9-13, 1986  
San Diego, California

**Special Prize Forum**

Paper entitled: Differential Pathways of  $3\alpha$   
Androstanediol Glucuronide ( $3\alpha$ diol G)  
Formation in Human Skin  
Presented at the 34th Annual Meeting of the  
Society for Gynecologic Investigation  
March 18-21, 1987, Atlanta, Georgia

**Special Prize Forum**

Paper entitled: Opiates Modulate the  
Inhibitory Effects of Androgen on the  
Hypothalamic-Pituitary Axis (HPA) of Normal Women  
Presented at the 34th Annual Meeting of the  
Society for Gynecologic Investigation  
March 18-21, 1987, Atlanta, Georgia

Serono Award (1st Prize)  
Paper entitled: Adrenal Effects of Short-Term  
Administration of Testosterone in Normal Women  
Presented at the 35th Annual Meeting of the  
Pacific Coast Fertility Society  
May 6-10, 1987, Palm Springs, California

Serono Award (2nd Prize)  
Paper entitled: Secretory Dynamics of  
Bioactive and Immunoreactive PRL in PCO  
Presented at the 35th Annual Meeting of the  
Pacific Coast Fertility Society, May 6-10, 1987  
Palm Springs, California

Outstanding Teacher Award, 1988  
Department of Family Medicine  
University of Southern California  
School of Medicine, Los Angeles, California

Serono Award (2nd Prize). Paper entitled: Decreased  
Responses of ACTH to Ovine Corticotropin-Releasing  
Factor (OCRF) and Increased Adrenal Insensitivity in  
Hyperandrogenic Women  
Presented at the 37th Annual Meeting of the  
Pacific Coast Fertility Society  
April 12-16, 1989, Palm Springs, California

Wyeth Award  
Paper entitled: Human Chorionic Gonadotropin (hCG)  
Enhances Progesterin Stimulation of Prolactin (PRL)  
Production by Human Endometrial Stromal Cells in  
Culture: Evidence for Trophoblast-Endometrial  
Interaction Presented at the 38th Annual

Paracrine  
Meeting of the

Pacific Coast Fertility Society  
April 25-29, 1990, Scottsdale, Arizona

Mead Johnson Laboratory/Purvis Martin, M.D.  
Research Award  
Paper entitled: Insulin Induced Stress  
Responses and the Effects of Estrogen and  
Progesterin in Postmenopausal Women (PMW)

Presented at the 39th Annual Meeting of the  
Pacific Coast Fertility Society, April 10-14, 1991  
Indian Wells, California

**Serono Award (1st Prize)**

**Paper entitled: The Synergistic Effects of  
Clomiphene Citrate and Human Menopausal  
Gonadotropins in Folliculogenesis of Hyperstimulated  
Cycles as Assessed by GnRH Antagonist (Nal-Glu)  
Presented at the 39th Annual Meeting of the  
Pacific Coast Fertility Society, April 10-14, 1991,  
Indian Wells, California**

**Serono Award (1st Prize)**

**Paper entitled: Assessing the Pharmacodynamic  
Properties of Exogenously Administered Progesterone:  
A comparison of Micronized Vaginal Delivery to  
Intramuscular Routes  
Presented at the 40th Annual Meeting of the  
Pacific Coast Fertility Society  
April 8-12, 1992, Indian Wells, California**

**Mead Johnson Laboratory/Purvis Martin, M.D.,  
Research Award**

**Paper entitled: The Route of Administration  
Influences the Effect of Estrogen on Insulin Sensitivity in  
Postmenopausal Women. Presented at the 41st Annual  
Meeting of the Pacific Coast Fertility Society, April 14-18,  
1993, Indian Wells, California**

**Serono Award (1st Prize)**

**Paper entitled: Serum AoG is a Useful Marker  
for the Treatment of Acne in Normoandrogenic Women  
Presented at the 42nd Annual Meeting of the  
Pacific Coast Fertility Society, April 20-24, 1994  
Indian Wells, California**

## PUBLICATIONS

Rogerio A. Lobo, M.D.

### Peer-Review Journals:

1. Lobo RA, Kletzky OA, Kaptein EM and Goebelsmann U: Prolactin modulation of dehydroepiandrosterone sulfate secretion. *Am J Obstet Gynecol* 138:632-636, 1980.
2. Lobo RA, March CM, Goebelsmann U, Krauss RM and Mishell DR Jr: Sub-dermal estradiol pellets following hysterectomy and oophorectomy. Effect upon serum estrone, estradiol, luteinizing hormone, follicle-stimulating hormone, corticosteroid binding globulin-binding capacity, testosterone-estradiol binding globulin-binding capacity, lipids, and hot flushes. *Am J Obstet Gynecol* 138:714-719, 1980.
3. Lobo RA and Goebelsmann U: Adult manifestation of congenital adrenal hyperplasia due to incomplete 21-hydroxylase deficiency mimicking polycystic ovarian disease. *Am J Obstet Gynecol* 138:720-726, 1980.
4. Lobo RA, Paul WL and Goebelsmann U: Dehydroepiandrosterone sulfate as an indicator of adrenal androgen function. *Obstet Gynecol* 57:69-73, 1981.
5. Lobo RA, Granger L, Goebelsmann U and Mishell DR Jr: Elevations in unbound serum estradiol as a possible mechanism for inappropriate gonadotropin secretion in women with PCO. *J Clin Endocrinol Metab* 52:156-158, 1981.
6. Lobo RA, Paul WL and Goebelsmann U: Serum levels of DHEAS in gynecologic endocrinopathy and infertility. *Obstet Gynecol* 57:607-612, 1981.
7. Lobo RA and Goebelsmann U: Evidence for reduced 3 $\beta$ -ol-hydroxysteroid dehydrogenase activity in some hirsute women thought to have polycystic ovary syndrome. *J Clin Endocrinol Metab* 53:394-400, 1981.
8. Lobo RA, March CM, Goebelsmann U and Mishell DR Jr: The modulating role of obesity and 17 $\beta$ -estradiol (E<sub>2</sub>) on bound and unbound E<sub>2</sub> and adrenal androgens in oophorectomized women. *J Clin Endocrinol Metab* 54:320-324, 1982.
9. Lobo RA, Gysler M, March CM, Goebelsmann U and Mishell DR Jr: Clinical and laboratory predictors of clomiphene response. *Fertil Steril* 37:168-174, 1982.
10. Lobo RA and Goebelsmann U: Effect of androgen excess on inappropriate gonadotropin secretion as found in the polycystic ovary syndrome. *Am J Obstet Gynecol* 142:394-401, 1982.
11. Lobo RA, Goebelsmann U, Brenner PF and Mishell DR Jr: The effects of estrogen on adrenal androgens in oophorectomized women. *Am J Obstet Gynecol* 142:471-478, 1982.
12. Horton R, Hawks D and Lobo R: 3 $\alpha$ , 17 $\beta$ -Androstenediol glucuronide in plasma: A marker of androgen action in idiopathic hirsutism. *J Clin Invest* 69:1203-1206, 1982.



13. Lobo RA, Granger LR, Davajan V and Mishell DR Jr: An extended regimen of clomiphene citrate in women unresponsive to standard therapy. *Fertil Steril* 37:762-766, 1982.
14. Lobo RA and Gibbons WE: The role of progestin therapy in breast disease and central nervous system function. *J Reprod Med* 27:515-521, 1982.
15. Lobo RA, Paul W, March CM, Granger L and Kletzky OA: Clomiphene and dexamethasone in women unresponsive to clomiphene alone. *Obstet Gynecol* 60:497-501, 1982.
16. Lahteenmaki P, Lobo R, Marrs RP, Gibbons WE, Nakamura RM and diZerega GS: Characterization of porcine granulosa cells by isopycnic gradient centrifugation. *Biol Reprod* 27:633-640, 1982.
17. Mashchak CA, Lobo RA, Dozono-Takano R, Eggena P, Nakamura RM, Brenner PF and Mishell DR Jr: Comparison of pharmacodynamic properties of various estrogen formulations. *Am J Obstet Gynecol* 144:511-518, 1982.
18. Shaaban MM, Hung TT, Hoffman DI, Lobo RA and Goebelsmann U:  $\beta$ -Endorphin and  $\beta$ -lipotropin concentrations in umbilical cord blood. *Am J Obstet Gynecol* 144:560-568, 1982.
19. Readhead C, Lobo RA and Kletzky OA: The activity of 3 $\beta$ -hydroxysteroid dehydrogenase and  $\nabla^{4,5}$  isomerase in human follicular tissue. *Am J Obstet Gynecol* 145:491-495, 1983.
20. Lobo RA, Granger LR, Paul WL, Goebelsmann U and Mishell DR Jr: Psychological stress and increases in urinary norepinephrine metabolites, platelet serotonin, and adrenal androgens in women with polycystic ovary syndrome. *Am J Obstet Gynecol* 145:496-503, 1983.
21. Lobo RA and Kletzky OA: Normalization of androgen and sex hormone-binding globulin levels after treatment of hyperprolactinemia. *J Clin Endocrinol Metab* 56:562-566, 1983.
22. Lobo RA, Kletzky OA, Campeau JD and diZerega GS: Elevated bioactive luteinizing hormone in women with the polycystic ovary syndrome. *Fertil Steril* 39:674-678, 1983.
23. Petruchia RA, Goebelsmann U, Hung TT, Haase HR and Lobo RA: Amniotic fluid  $\beta$ -endorphin and  $\beta$ -lipotropin concentrations during the second and third trimester. *Am J Obstet Gynecol* 146:644-651, 1983.
24. Lobo RA, Brenner P and Mishell DR Jr: Metabolic parameters and steroid levels in postmenopausal women receiving lower doses of natural estrogen replacement. *Obstet*

Gynecol 62:94-98, 1983.

25. Lobo RA, Goebelsmann U and Horton R: Evidence for the importance of peripheral tissue events in the development of hirsutism in polycystic ovary syndrome. *J Clin Endocrinol Metab* 57:393-397, 1983.
26. diZerega GS, Campeau JD, Nakamura RM, Ujita EL, Lobo R and Marrs RP: Activity of a human follicular fluid protein(s) in spontaneous and induced ovarian cycles. *J. Clin Endocrinol Metab* 57:838-846, 1983.
27. Shoupe D, Kumar DD and Lobo R: Insulin resistance in polycystic ovary syndrome. *Am J Obstet Gynecol* 147:588-592, 1983.
28. diZerega GS, Campeau JD, Ujita EL, Kling OR, Marrs RP, Lobo RA and Nakamura RM: The possible role for a follicular protein in the intraovarian regulation of folliculogenesis. *Sem Reprod Endocrinol* 1:309-320, 1983.
29. Lobo RA, McCormick W, Singer F and Roy S: Depo-medroxyprogesterone acetate compared with conjugated estrogens for the treatment of postmenopausal women. *Obstet Gynecol* 63:1-5, 1984.
30. Lobo RA, Shoupe D, Chang SP and Campeau J: The control of bioactive luteinizing hormone secretion in women with polycystic ovary syndrome. *Am J Obstet Gynecol* 148:423-428, 1984.
31. Shoupe D, and Lobo RA: The influence of androgens on insulin resistance. *Fertil Steril* 41:385-388, 1984.
32. Levitan D, Moser SA, Goldstein DA, Kletzky OA, Lobo RA and Massry SG: Disturbances in the hypothalamic-pituitary-gonadal axis in male patients with acute renal failure. *Am J Nephrol* 4:99-106, 1984.
33. Marrs RP, Lobo R, Campeau JD, Nakamura RM, Brown J, Ujita EL and diZerega GS: Correlation of human follicular fluid inhibin activity with spontaneous and induced follicle maturation. *J Clin Endocrinol Metab* 58:704-709, 1984.
34. Klove KL, Roy S and Lobo RA: The effect of different contraceptive treatments on the serum concentration of dehydroepiandrosterone sulfate. *Contraception* 29:319-324, 1984.
35. Chang SP, Shoupe D, Kletzky OA, Lobo RA: Differences in the ratio of bioactive to immunoreactive serum luteinizing hormone during vasomotor flushes and hormonal therapy in postmenopausal women. *J Clin Endocrinol Metab* 58:925-929, 1984.
36. diZerega GS, Marrs RP, Lobo R, Ujita EL, Brown J and Campeau JD: Correlation of inhibin and follicle regulatory protein activities with follicular fluid steroid levels in anovulatory patients. *Fertil Steril* 41:849-855, 1984.

37. Lobo RA, Shoupe D, Roy S and Paul W: Central and peripheral metabolites of norepinephrine and dopamine in postmenopausal women. *Am J Obstet Gynecol* 149:548-552, 1984.
38. Hoffman DI, Klove K and Lobo RA: The prevalence and significance of elevated dehydroepiandrosterone sulfate levels in anovulatory women. *Fertil Steril* 42:76-81, 1984.
39. Fallis RJ, Fisher M and Lobo RA: A double blind trial of naloxone in the treatment of acute stroke. *Stroke* 15:627-629, 1984.
40. Shoupe D and Lobo RA: Evidence for altered catecholamine metabolism in polycystic ovary syndrome. *Am J Obstet Gynecol* 150:566-571, 1984.
41. Lobo RA, diZerega GS and Marrs RP: Follicular fluid steroid levels in dysmature and mature follicles from spontaneous and hyperstimulated cycles in normal and anovulatory women. *J Clin Endocrinol Metab* 60:81-87, 1985.
42. Shoupe D, Montz FJ and Lobo RA: The effects of estrogen and progestin on endogenous opioid activity in oophorectomized women. *J Clin Endocrinol Metab* 60:178-183, 1985.
43. Serafini P and Lobo RA: Increased  $5\alpha$ -reductase activity in idiopathic hirsutism. *Fertil Steril* 43:74-78, 1985.
44. Serafini P, Ablan F and Lobo RA:  $5\alpha$ -Reductase activity in the genital skin of hirsute women. *J Clin Endocrinol Metab* 60:349-355, 1985.
45. Hoffman D and Lobo RA: Serum dehydroepiandrosterone sulfate and the use of clomiphene citrate in anovulatory women. *Fertil Steril* 43:196-199, 1985.
46. Lobo RA, Shoupe D, Serafini P, Brinton D and Horton R: The effects of two doses of spironolactone on serum androgens and anagen hair in hirsute women. *Fertil Steril* 43:200-205, 1985.
47. Shoupe D and Lobo RA: Prolactin response after gonadotropin-releasing hormone in the polycystic ovary syndrome. *Fertil Steril* 43:549-553, 1985.
48. Hoffman DI, Lobo RA, Campeau JD, Jsai H-M, Holmberg EA, Ono T, Frederick JL, Platt LD and diZerega GS: Ovulation induction in clomiphene-resistant anovulatory women: Differential follicular response to purified urinary follicle-stimulating hormone (FSH) versus purified urinary FSH and luteinizing hormone. *J Clin Endocrinol Metab* 60:922-927, 1985.

49. Lobo RA, Roy S, Shoupe D, Endres DB, Adams JS, Rude RK and Singer FR: Estrogen and progestin effects on urinary calcium and calciotropic hormones in surgically-induced postmenopausal women. *Horm Metab Res* 17:369-372, 1985.
50. Serafini PC, Catalino J and Lobo RA: The effect of spironolactone on genital skin  $5\alpha$ -reductase activity. *J Steroid Biochem* 23:191-194, 1985.
51. Barnes DB, and Lobo RA: Comparison of lipid and androgen levels after conjugated estrogen or depo-medroxyprogesterone acetate treatment in postmenopausal women. *Obstet Gynecol* 66:216-219, 1985.
52. Barnes RB, and Lobo RA: Central opioid activity in polycystic ovary syndrome with and without dopaminergic modulation. *J Clin Endocrinol Metab* 61:779-782, 1985.
53. Mashchak CA and Lobo RA: Estrogen replacement therapy and hypertension. *J Reprod Med (Suppl 10)* 30:805-810, 1985.
54. Chiang RS, Barnes RB, Shoupe D and Lobo RA: Dose-related changes in LH bioactivity with intranasal GnRH agonist administration. *Contraception* 32:342-357, 1985.
55. Serafini P and Lobo RA: The effects of spironolactone on adrenal steroidogenesis in hirsute women. *Fertil Steril* 44:595-599, 1985.
56. Serafini P, and Lobo RA: Prolactin modulates peripheral androgen metabolism. *Fertil Steril* 45:41-46, 1986.
57. Barnes RB, Cha K-Y, Lee DG and Lobo RA: Modulation of luteinizing hormone immunoreactivity and bioactivity by dopamine but not norepinephrine in women. *Am J Obstet Gynecol* 154:445-450, 1986.
58. Gibbons WE, Moyer DL, Lobo RA, Roy S and Mishell DR Jr: Biochemical and histologic effects of sequential estrogen/progestin therapy on the endometrium of postmenopausal women. *Am J Obstet Gynecol* 154:456-461, 1986.
59. Cha KY, Barnes RB, Marrs RP and Lobo RA: Correlation of the bioactivity of luteinizing hormone in follicular fluid with oocyte maturity in the spontaneous cycle. *Fertil Steril* 45:338-341, 1986.
60. Steingold KA, Lobo RA, Judd HL, Lu JKH and Chang RJ: The effect of bromocriptine on gonadotropin and steroid secretion in polycystic ovarian disease. *J Clin Endocrinol Metab* 62:1048-1051, 1986.
61. Barnes RB, Mileikowsky GN, Cha, KY, Spencer CA and Lobo RA: Effects of dopamine

- and metoclopramide in polycystic ovary syndrome. *J Clin Endocrinol Metab* 63:506-509, 1986.
62. Paulson RJ, Serafini PC, Catalino JA and Lobo RA: Measurements of  $3\alpha$ , 17 $\beta$ -androstenediol glucuronide in serum and urine and the correlation with skin  $5\alpha$ -reductase activity. *Fertil Steril* 46:222-226, 1986.
  63. Paulson RJ, Bernstein GS, Marrs RP and Lobo RA: Idiopathic oligospermia and peripheral androgen metabolism. *Fertil Steril* 46:480-483, 1986.
  64. Serafini P, Silva PD, Paulson RJ, Elkind-Hirsch K, Hernandez M and Lobo RA: Acute modulation of the hypothalamic-pituitary axis by intravenous testosterone in normal women. *Am J Obstet Gynecol* 155:1288-1292, 1986.
  65. Silva PD, Paulson RJ, Anderson RE and Lobo RA: Ectopic pregnancy in unrepaired distal tubal remnant after contralateral tubal anastomosis. *Fertil Steril* 47:522-523, 1987.
  66. Bernstein L, Ross RK, Lobo RA, Hanisch R, Krailo MD and Henderson BE: The effects of moderate physical activity on menstrual cycle patterns in adolescence: Implications for breast cancer prevention. *Br J Cancer* 55:681-685, 1987.
  67. Kaufman FR, Donnell GN and Lobo RA: Ovarian androgen secretion in patients with galactosemia and premature ovarian failure. *Fertil Steril* 47:1033-1034, 1987.
  68. Barnes RB, Artal R and Lobo RA: Peripheral dopamine metabolism in polycystic ovary syndrome. *Obstet Gynecol* 70:153-156, 1987.
  69. Silva PD, Gentzschein EEK and Lobo RA: Androstenedione may be a more important precursor of tissue dihydrotestosterone than testosterone in women. *Fertil Steril* 48:419-422, 1987.
  70. Serafini P, Paulson RJ, Francis MM and Lobo RA: Modulation of prolactin responses to gonadotropin releasing hormone by acute testosterone infusions in normal women. *Gynecol Endocrinol* 1:247-253, 1987.
  71. Lobo RA, Paul WL, Gentzschein E, Serafini PC, Catalino JA, Paulson RJ and Horton R: Production of  $3\alpha$ -androstenediol glucuronide in human genital skin. *J Clin Endocrinol Metab* 65:711-714, 1987.
  72. Rosen GF, Vermesh M, d'Ablain G III, Wachtel S and Lobo RA: The endocrinologic evaluation of a 45,X true hermaphrodite. *Am J Obstet Gynecol* 157:1272-1273, 1987.
  73. Rosen GF and Lobo RA: Further evidence against dopamine deficiency as the cause of inappropriate gonadotropin secretion in patients with polycystic ovary syndrome. *J Clin*

Endocrinol Metab 65:891-895, 1987.

74. Vermesh M, Silva PD and Lobo RA: Endogenous opioids modulate the inhibitory effects of androgen on the hypothalamic-pituitary axis of normal women. *J Clin Endocrinol Metab* 65:1183-1186, 1987.
75. Shoupe D, Mishell DR Jr, Page MA, Madkour H, Spitz IM and Lobo RA: Effects of antiprogesterone RU 486 in normal women. II. Administration in the late follicular phase. *Am J Obstet Gynecol* 157:1421-1426, 1987.
76. Vermesh M, Silva PD, Rosen GF, Vijod AG and Lobo RA: Effect of androgen on adrenal steroidogenesis in normal women. *J Clin Endocrinol Metab* 66:128-130, 1988.
77. Lobo RA, Nguyen HN, Eggena P and Brenner PF: Biologic effects of equilin sulfate in postmenopausal women. *Fertil Steril* 49:234-238, 1988.
78. Anderson RE, Ben-Rafael Z, Flickinger GL, Meloni F, Barnes RB, Rosen GF and Lobo RA: Secretory dynamics of bioactive and immunoreactive prolactin in polycystic ovary syndrome. *Fertil Steril* 49:239-243, 1988.
79. Silva PD, Porto M, Moyer DL and Lobo RA: Clinical and ultrastructural findings of an androgenizing Krukenberg tumor in pregnancy. *Obstet Gynecol* 71:432-434, 1988.
80. Davidson A, Vermesh M, Lobo RA and Paulson RJ: Mouse embryo culture as quality control for human in vitro fertilization: The one-cell versus the two-cell model. *Fertil Steril* 49:516-521, 1988.
81. Do YS, Sherrod A, Lobo RA, Paulson RJ, Shinagawa T, Chen S, Kjos S and Hseuh WA: Human ovarian theca cells are a source of renin. *Proc Natl Acad Sci* 85:1957-1961, 1988.
82. Pasupuleti V, Lobo R and Horton R: Conversion of dihydro-testosterone to androstanediol glucuronide by female sexual skin. *Steroids* 51:269-282, 1988.
83. Rosen GF, Kaplan B and Lobo, RA: Menstrual function and hirsutism in patients with gonadal dysgenesis. *Obstet Gynecol* 71:677-680, 1988.
84. Henderson BE, Pike MC, Ross RK, Mack TM and Lobo R: Re-evaluating the role of progestogen therapy after the menopause. *Fertil Steril (Suppl 5)* 49:9-15, 1988.
85. Paulson RJ, Lobo RA, Stein A, Toker R, Moegle A and Macasos T: Gestation of triplets after intrauterine implantation of two embryos. *N Eng J Med* 318:1339-1340, 1988.
86. Davidson A, Vermesh M, Lobo RA and Paulson RJ: The temporal effects of changes in in vitro fertilization culture media on the one-cell mouse embryo system. *J In Vitro*

- Fertil Embryo Transfer 5:149-152, 1988.
87. Lobo, RA: Lipids, clotting factors, and diabetes: Endogenous risk factors for cardiovascular disease. *Am J Obstet Gynecol* 158:1584-1605, 1988.
  88. Silva RD, Richmond JA and Lobo RA: Diagnosis and management of a tuberculous, tuboappendiceal fistula. *Am J Obstet Gynecol* 159:440-441, 1988.
  89. Paulson RJ and Lobo RA: Ovarian hyperstimulation complicating the clinical presentation of a pre-existing ectopic pregnancy. *Fertil Steril* 50:670-671, 1988.
  90. Rodriguez MH, Platt LD, Medearis AL, Lacarra M and Lobo RA: The use of transvaginal sonography for evaluation of postmenopausal ovarian size and morphology. *Am J Obstet Gynecol* 159:810-814, 1988.
  91. Vermesh M, Silva PD, Sauer MV, Vargyas JM and Lobo RA: Persistent tubal ectopic gestation: Patterns of circulating  $\beta$ -human chorionic gonadotropin and progesterone, and management options. *Fertil Steril* 50:584-588, 1988.
  92. Lobo RA: The androgenicity of progestational agents. *Int J Fertil (Suppl)* 33:6-12, 1988.
  93. Whitehead M and Lobo RA: Progestogen use in postmenopausal women. *The Lancet* II:1243-1244, 1988.
  94. Sauer MV, Vermesh M, Anderson RE, Vijod AG, Stanczyk FZ and Lobo RA: Rapid measurement of urinary pregnanediol glucuronide to diagnose ectopic pregnancy. *Am J Obstet Gynecol* 159:1531-1535, 1988.
  95. Stanczyk FZ, Shoupe D, Nunez V, Macias-Gonzales P, Vijod MA and Lobo RA: A randomized comparison of nonoral estradiol delivery in postmenopausal women. *Am J Obstet Gynecol* 159:1540-1546, 1988.
  96. Paulson RJ, Do YS, Hsueh WA and Lobo RA: Gradients of prorenin and active renin in ovarian venous and peripheral venous blood samples obtained simultaneously. *Am J Obstet Gynecol* 159:1575-1579, 1988.
  97. Shoupe D, Mishell DR Jr, Lacarra M, Lobo RA, Horenstein J, d'Ablaing G and Moyer D: Correlation of endometrial maturation with four methods of estimating day of ovulation. *Obstet Gynecol* 73:88-92, 1989.
  98. Bernstein L, Pike MC, Lobo RA, Depue RH, Ross RK and Henderson BE: Cigarette smoking in pregnancy results in marked decrease in maternal hCG and oestradiol levels. *Br J Obstet Gynaecol* 96:92-96, 1989.
  99. Lobo RA and Whitehead M: Too much of a good thing? Use of progestogens in the menopause: An international consensus statement. *Fertil Steril* 51:229-231, 1989.

100. Kaufman FR, Xu YK, Ng W, Silva PD, Lobo RA and Donnell G: Gonadal function and ovarian galactose metabolism in classical galactosemia. *Acta Endocrinol* 120:129-133, 1989.
101. Xu Y-K, Ng WG, Kaufman FR, Lobo RA and Donnell GN: Galactose metabolism in human ovarian tissue. *Pediatr Res* 25:151-155, 1989.
102. Ross RK, Pike MC, Henderson BE, Mack TM and Lobo RA: Stroke prevention and oestrogen replacement therapy. *The Lancet* I:505, 1989.
103. Paulson RJ, Do YS, Hsueh WA, Eggena P and Lobo RA: Ovarian renin production in vitro and in vivo: Characterization and clinical correlation. *Fertil Steril* 51:634-638, 1989.
104. Davidson A, Vermesh M, Paulson RJ, Graczykowski JW and Lobo RA: Presence of immunoreactive  $\beta$ -endorphin and calcitonin in human seminal plasma, and their relation to sperm physiology. *Fertil Steril* 51:878-880, 1989.
105. Paulson RJ, Sauer MV and Lobo RA: In vitro fertilization in unstimulated cycles: A new application. *Fertil Steril* 51:1059-1060, 1989.
106. Anderson RE, Cragun JM, Chang RJ, Stanczyk FZ and Lobo RA: A pharmacodynamic comparison of human urinary follicle-stimulating hormone and human menopausal gonadotropin in normal women and polycystic ovary syndrome. *Fertil Steril* 52:216-220, 1989.
107. Sauer MV, Lobo RA and Paulson RJ: Successful twin pregnancy after embryo donation to a patient with XY gonadal dysgenesis. *Am J Obstet Gynecol* 161:380-381, 1989.
108. Pike MC, Ross RK, Lobo RA, Key TJA, Potts M and Henderson, BE: LHRH agonists and the prevention of breast and ovarian cancer. *Br J Cancer* 60:142-148, 1989.
109. Sauer MV, Paulson RJ, Macaso TM, Francis-Hernandez M and Lobo RA: Establishment of a nonanonymous donor oocyte program: Preliminary experience at the University of Southern California. *Fertil Steril* 52:433-436, 1989.
110. Steinleitner A, Stanczyk FZ, Levin JH, d'Ablaing G III, Vijod MA, Shahbazian VL and Lobo RA: Decreased in vitro production of 6-keto-prostaglandin  $F_{1\alpha}$  by uterine arteries from postmenopausal women. *Am J Obstet Gynecol* 161:1677-1681, 1989.
111. Matteri RK, Stanczyk FZ, Gentzschein EE, Delgado C and Lobo RA: Androgen sulfate and glucuronide conjugates in nonhirsute and hirsute women with polycystic ovarian syndrome. *Am J Obstet Gynecol* 161:1704-1709, 1989.
112. Sauer MV, Paulson RJ and Lobo RA: Simultaneous establishment of pregnancies in two ovarian failure patients using one oocyte donor. *Fertil Steril* 52:1072-1073, 1989.



113. Stanczyk FZ, Lobo RA, Chiang ST and Woutersz TB: Pharmacokinetic comparison of two triphasic oral contraceptive formulations containing levonorgestrel and ethinylestradiol. *Contraception* 41:39-53, 1990.
114. Graczykowski JW, Vermesh M, Siegel MS, Davidson A and Lobo RA: Absence of direct effect of beta-endorphin and calcitonin on human sperm motility. *Arch Androl* 24:121-124, 1990.
115. Sauer MV, Paulson RJ and Lobo RA: Successful pre-embryo donation in ovarian failure after treatment for breast carcinoma. *The Lancet* 335:723, 1990.
116. Lobo RA: Cardiovascular implications of estrogen replacement therapy. *Obstet Gynecol* (Suppl 4) 75:18S-25S, 1990.
117. Paulson RJ, Sauer MV and Lobo RA: Embryo implantation after human in vitro fertilization: Importance of endometrial receptivity. *Fertil Steril* 53:870-874, 1990.
118. Carmina E and Lobo RA: Pituitary-adrenal responses to corticotropin-releasing factor in late onset 21-hydroxylase deficiency. *Fertil Steril* 54:79-83, 1990.
119. Anderson RE, Stein AL, Paulson RJ, Stanczyk FZ, Vijod AG and Lobo RA: Effects of norethindrone on gonadotropin and ovarian steroid secretion when used for cycle programming during in vitro fertilization. *Fertil Steril* 54:96-101, 1990.
120. Carmina E, Levin JH, Malizia G and Lobo RA: Ovine corticotropin-releasing factor and dexamethasone responses in hyperandrogenic women. *Fertil Steril* 54:245-250, 1990.
121. Kaufman FR, Stanczyk FZ, Matteri RK, Gentzsch E, Delgado C and Lobo RA: Dehydroepiandrosterone and dehydro-epiandrosterone sulfate metabolism in human genital skin. *Fertil Steril* 54:251-254, 1990.
122. Bernstein L, Yuan J-M, Ross RK, Pike MC, Hanisch R, Lobo R, Stanczyk F, Gao Y-T and Henderson BE: Serum hormone levels in pre-menopausal Chinese women in Shanghai and White women in Los Angeles: Results from two breast cancer case-control studies. *Cancer Causes and Controls* 1:51-58, 1990.
123. Lobo RA: Adult onset 21-hydroxylase deficiency: A significant problem in gynecology? *Gynecol Report* 2:266-272, 1990.
124. Stanczyk FZ, Matteri RK, Kaufman FR, Gentzsch E and Lobo RA: Androstenedione is an important precursor of dihydro-testosterone in the genital skin of women and is metabolized via 5 $\alpha$ -androstenedione. *J Steroid Biochem Molec Biol* 37:129-132, 1990.
125. Paulson RJ, Sauer MV, and Lobo RA: Pregnancy after in vitro fertilization in a patient with stage I endometrial carcinoma treated with progestins. *Fertil Steril* 54:735-736, 1990.

126. Sauer MV, Paulson RJ and Lobo RA: A preliminary report on oocyte donation extending reproductive potential to women over 40. *N Eng J Med* 323:1157-1160, 1990.
127. Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: In vitro fertilization in unstimulated cycles: A clinical trial utilizing hCG for timing of follicle aspiration. *Obstet Gynecol* 76:788-791, 1990.
128. Carmina E and Lobo RA: Pituitary-adrenal responses to ovine corticotropin-releasing factor in polycystic ovary syndrome and in other hyperandrogenic patients. *Gynecol Endocrinol* 4:225-232, 1990.
129. Levin JH, Tonetta SA and Lobo RA: Comparison of norethindrone and medroxy-progesterone acetate with natural progesterone and estradiol in stimulating prolactin production from cultured endometrial stromal cells. *Am J Obstet Gynecol* 163:1932-1938, 1990.
130. Cassidenti DL, Vijod AG, Vijod MA, Stanczyk FZ and Lobo RA: Short-term effects of smoking on the pharmacokinetic profiles of micronized estradiol in postmenopausal women. *Am J Obstet Gynecol* 163:1953-1960, 1990.
131. Shoupe D, Mishell DR Jr, Fossum G, Bopp BL, Spitz IM and Lobo RA: Antiprogestin treatment decreases midluteal luteinizing hormone pulse amplitude and primarily exerts a pituitary inhibition. *Am J Obstet Gynecol* 163:1982-1985, 1990.
132. Paulson RJ, Sauer MV and Lobo RA: Factors affecting embryo implantation after human in vitro fertilization: A hypothesis. *Am J Obstet Gynecol* 163:2020-2023, 1990.
133. Sauer MV, Paulson RJ, Macaso TM, Francis MM and Lobo RA: Oocyte and pre-embryo donation to women with ovarian failure: An extended clinical trial. *Fertil Steril* 55:39-43, 1991.
134. Frederick JL, Francis MM, Macaso TM, Lobo RA, Sauer MV and Paulson RJ: Preovulatory follicular fluid steroid levels in stimulated and unstimulated cycles triggered with human chorionic gonadotropin. *Fertil Steril* 55:44-47, 1991.
135. Carmina E, Stanczyk FZ, Matteri RK, and Lobo RA: Serum androsterone conjugates differentiate between acne and hirsutism in hyperandrogenic women. *Fertil Steril* 55:872-876, 1991.
136. Sauer MV, Kaufman FR, Paulson RJ and Lobo RA: Pregnancy after oocyte donation to a woman with ovarian failure and classical galactosemia. *Fertil Steril* 55:1197-1199, 1991.
137. Cassidenti DL, Paulson RJ, Serafini P, Stanczyk FZ and Lobo RA: Effects of sex steroids on skin 5 $\alpha$ -reductase activity in vitro. *Obstet Gynecol* 78:103-107, 1991.

138. Presser SC, Stanczyk FZ and Lobo RA: Simultaneous measurements of prostacyclin and thromboxane metabolites during the menstrual cycle. *Am J Obstet Gynecol* 165:647-651, 1991.
139. Koonings PP, Al-Marayati L, Schlaerth JB and Lobo RA: Mayer-Rokitansky-Kuster-Hauser syndrome associated with endodermal sinus tumor of the ovary. *Fertil Steril* 56:577-578, 1991.
140. Levin JH, Carmina E and Lobo RA: Is the inappropriate gonadotropin secretion of patients with polycystic ovary syndrome similar to that of patients with adult onset congenital adrenal hyperplasia? *Fertil Steril* 56:635-640, 1991.
141. Ditkoff EC and Lobo RA: Ovarian stimulation. *Curr Opin Obstet Gynecol* 3:635-640, 1991.
142. Lobo RA: Effects of hormonal replacement on lipids and lipoproteins in postmenopausal women. *J Clin Endocrinol Metab* 73:925-930, 1991.
143. Carmina E and Lobo RA: Peripheral androgen blockade versus glandular androgen suppression in the treatment of hirsutism. *Obstet Gynecol* 78:845-849, 1991.
144. Ditkoff EC, Crary WG, Crisito M and Lobo RA: Estrogen improves psychological function in asymptomatic post-menopausal women. *Obstet Gynecol* 78:991-995, 1991.
145. Cassidenti DL, Sauer MV, Paulson RJ, Ditkoff EC, Rivier J, Yen SSC and Lobo RA: Comparison of intermittent and continuous use of a gonadotropin-releasing hormone antagonist (Nal-Glu) in in-vitro fertilization cycles: A preliminary report. *Am J Obstet Gynecol* 165:1806-1810, 1991.
146. Ditkoff EC, Cassidenti DL, Paulson RJ, Sauer MV, Paul WL, Rivier J, Yen SSC and Lobo RA: The gonadotropin-releasing hormone antagonist (Nal-Glu) acutely blocks the luteinizing hormone surge but allows for resumption of folliculogenesis in normal women. *Am J Obstet Gynecol* 165:1811-1817, 1991.
147. Bergman A, Stanczyk FZ and Lobo RA: The role of prostaglandins in detrusor instability. *Am J Obstet Gynecol* 165:1833-1836, 1991.
148. Stanczyk FZ, Chang L, Carmina E, Putz Z and Lobo RA: Is 11 $\beta$ -hydroxyandrostenedione a better marker of adrenal androgen excess than dehydroepiandrosterone sulfate? *Am J Obstet Gynecol* 165:1837-1842, 1991.
149. Shoupe D, Meme D, Mezrow G, Lobo RA: Prevention of endometrial hyperplasia in postmenopausal women with intrauterine progesterone. *N Engl J Med* 325:1811-2, 1991.
150. Lobo RA and Cassidenti DL: Pharmacokinetics of oral 17 $\beta$ -estradiol. *J Reprod Med* 37:77-84, 1992.

151. Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: In vitro fertilization in unstimulated cycles: the University of Southern California experience. *Fertil Steril* 57:290-293, 1992.
152. Lobo RA: Estrogen and the risk of coagulopathy. *Am J Med* 92:283-285, 1992.
153. Lobo RA, Notelovitz M, Bernstein L, Khan FY, Ross RK and Paul WL: Lp (a) lipoprotein: Relationship to cardiovascular disease risk factors, exercise, and estrogen. *Am J Obstet Gynecol* 166:1182-1190, 1992.
154. Cassidenti DL, Paulson RJ, Lobo RA and Sauer MV: The synergistic effects of ciomiphene citrate and human menopausal gonadotrophin in the folliculogenesis of stimulated cycles as assessed by the gonadotrophin-releasing hormone antagonist Nal-Glu. *Hum Reprod* 7:344-348, 1992.
155. Ross RK, Bernstein L, Lobo RA, Shimizu H, Stanczyk FZ, Pike MC and Henderson BE: 5-Alpha-reductase activity and risk of prostate cancer among Japanese and US white and black males. *The Lancet* 339:887-889, 1992.
156. Cassidenti DL, Pike MC, Vijod AG, Stanczyk FZ and Lobo RA: A reevaluation of estrogen status in postmenopausal women who smoke. *Am J Obstet Gynecol* 166:1444-1448, 1992.
157. Lobo RA: The role of progestins in hormone replacement therapy. *Am J Obstet Gynecol* 166:1997-2004, 1992.
158. Carmina E, Stanczyk FZ, Chang L, Miles RA and Lobo RA: The ratio of androstenedione: 11 $\beta$ -hydroxyandrostenedione is an important marker of adrenal androgen excess in women. *Fertil Steril* 58:148-152, 1992.
159. Sauer MV, Paulson RJ and Lobo RA: Reversing the natural decline in human fertility: An extended clinical trial of oocyte donation to women of advanced reproductive age. *JAMA* 268:1275-1279, 1992.
160. Levin JH, Stanczyk FZ and Lobo RA: Estradiol stimulates the secretion of prostacyclin and thromboxane from endometrial stromal cells in culture. *Fertil Steril* 58:530-536, 1992.
161. Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: A prospective controlled evaluation of TEST-yolk buffer in the preparation of sperm for human in vitro fertilization in suspected case of male infertility. *Fertil Steril* 58:551-555, 1992.
162. Miles RA, Cassidenti DL, Carmina E, Gentzschein E, Stanczyk FZ and Lobo RA:

- Cutaneous application of an androstenedione gel as an in vivo test of  $5\alpha$ -reductase activity in women. *Fertil Steril* 58:708-712, 1992.
163. Matteri RK, Stanczyk FZ, Cassidenti DL, Paulson RJ and Lobo RA: The ovarian contribution to peripherally derived serum C<sup>19</sup> conjugates. *J Clin Endocrinol Metab* 75:768- 772, 1992.
  164. Carmina E, Koyama T, Chang L, Stanczyk FZ and Lobo RA: Does ethnicity influence the prevalence of adrenal hyperandrogenism and insulin resistance in polycystic ovary syndrome? *Am J Obstet Gynecol* 167:1807-1812, 1992.
  165. Carmina E, Ditkoff EC, Malizia G, Vijod AG, Janni A and Lobo RA: Increased circulating levels of immunoreactive  $\beta$ -endorphin in polycystic ovary syndrome is not caused by increased pituitary secretion. *Am J Obstet Gynecol* 167:1819-1824, 1992.
  166. Lindheim RS, Legro RS, Bernstein L, Stanczyk FZ, Vijod MA, Presser SC and Lobo RA: Behavioral stress responses in premenopausal and postmenopausal women and the effects of estrogen. *Am J Obstet Gynecol* 167:1831-1836, 1992.
  167. Ditkoff EC, Levin LH, Paul WL and Lobo RA: Time-resolved fluoroimmunoassay compared with radioimmunoassay of luteinizing hormone. *Fertil Steril* 59:305-310, 1993.
  168. Sauer MV, Paulson RJ and Lobo RA: Pregnancy after age 50: Application of oocyte donation to women after natural menopause. *The Lancet* 341:321-323, 1993.
  169. Lobo RA: Unexplained infertility. *J Reprod Med* 38:241-249, 1993.
  170. Carmina E and Lobo RA: Evidence for increased androsterone metabolism in some normoandrogenic women with acne. *J Clin Endocrinol Metab* 76:1111-1114, 1993.
  171. Price TM, Dupuis RE, Carr BR, Stanczyk FZ, Lobo RA and Droegemueller W: Single- and multiple-dose pharmacokinetics of a low-dose oral contraceptive in women with chronic renal failure undergoing peritoneal dialysis. *Am J Gynecol* 168:1400-1406, 1993.
  172. Lobo RA: Hormone replacement therapy: Oestrogen replacement after treatment for breast cancer? *The Lancet* 341:1313-1314, 1993.
  173. Sullivan JM and Lobo RA: Considerations for contraception in women with cardiovascular disorders. *Am J Obstet Gynecol* 168:2006-2011, 1993.
  174. Lindheim SR, Presser SC, Ditkoff EC, Vijod MA, Stanczyk FZ and Lobo RA: A possible bimodal effect of estrogen on insulin sensitivity in postmenopausal women and the attenuating effect of added progestin. *Fertil Steril* 60:664-667, 1993.
  175. Kojima T, Lindheim SR, Duffy DM, Vijod MA, Stanczyk FZ and Lobo RA: Insulin

- sensitivity is decreased in normal women by doses of ethinyl estradiol used in oral contraceptives. *Am J Obstet Gynecol* 169:1540-1544, 1993.
176. Carmina E, Janni A and Lobo RA: Physiological estrogen replacement may enhance the effectiveness of the gonadotropin-releasing hormone agonist in the treatment of hirsutism. *J Clin Endocrinol Metab* 78:126-130, 1994.
  177. Paulson RJ, Sauer MV and Lobo RA: Addition of a gonadotropin releasing hormone (GnRH) antagonist and exogenous gonadotropins to unstimulated in vitro fertilization (IVF) cycles: Physiologic observations and preliminary experience. *J Assist Reprod Genet* 11:28-32, 1994.
  178. Lindheim SR, Legro RS, Morris RS, Wong IL, Tran DQ, Vijod MA, Stanczyk FZ and Lobo RA: The effect of progestins on behavioral stress responses in postmenopausal women. *J Soc Gynecol Invest* 1:79-83, 1994.
  179. Lindheim SR, Notelovitz M, Feldman EB, Larsen S, Khan FY and Lobo RA: The independent effects of exercise and estrogen on lipids and lipoproteins in postmenopausal women. *Obstet Gynecol* 83:167-172, 1994.
  180. Sauer MV, Paulson RJ, Ary BA and Lobo RA: Three hundred cycles of oocyte donation at the University of Southern California: Assessing the effect of age and infertility diagnosis on pregnancy and implantation rates. *J Assist Reprod Genet* 11:92-96, 1994.
  181. Morris RS, Francis MM, Do YS, Hsueh WA, Lobo RA and Paulson RJ: Angiotensin II (AII) modulation of steroidogenesis by luteinized granulosa cells in vitro. *J Assist Reprod Genet* 11:117-122, 1994.
  182. Lobo RA and Speroff L: International consensus conference on postmenopausal hormone therapy and the cardiovascular system. *Fertil Steril* 61:592-595, 1994.
  183. Lindheim SR, Buchanan TA, Duffy DM, Vijod MA, Kojima T, Stanczyk FZ and Lobo RA: Comparison of estimates of insulin sensitivity in pre-and postmenopausal women using the insulin tolerance test and the frequently sampled intravenous glucose tolerance test. *J Soc Gynecol Invest* 1:150-154, 1994.
  184. Legro RS, Shahbahrani B, Lobo RA and Kovacs BW: Size polymorphisms of the androgen receptor among female Hispanics and correlation with androgenic characteristics. *Obstet Gynecol* 83:701-706, 1994.
  185. Speroff, L and Lobo RA: Postmenopausal hormone therapy and the cardiovascular system. *Heart Dis Stroke* 3:173-176, 1994.
  186. Lobo RA and Stanczyk FZ: New knowledge in the physiology of hormonal contraceptives. *Am J Obstet Gynecol* 170:1499-1507, 1994.

187. Legro RS, Dietz GW, Comings DE, Lobo RA and Kovacs BW: Association of dopamine D<sub>2</sub> receptor gene haplotypes with anovulation and fecundity in female Hispanics. *Hum Reprod* 9:1271-1275, 1994.
188. Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: Factors affecting pregnancy success of human in-vitro fertilization in unstimulated cycle. *Hum Reprod* 9:1571-1575, 1994.
189. Miles RA, Paulson RJ, Lobo RA, Press MF, Dahmouch L and Sauer MV: Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: A comparative study. *Fertil Steril* 62:485-490, 1994.
190. Carmina E and Lobo RA: Ovarian suppression reduces clinical and endocrine expression of late-onset congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Fertil Steril* 62:738-743, 1994.
191. Legro RS, Carmina E, Stanczyk FZ, Gentzsch E and Lobo RA: Alterations in androgen conjugate levels in women and men with alopecia. *Fertil Steril* 62:744-750, 1994.
192. Mezrow G, Shoupe D, Spicer D, Lobo RA, Leung B and Pike M: Depot leuprolide acetate with estrogen and progestin add-back for long-term treatment of premenstrual syndrome. *Fertil Steril* 62:932-937, 1994.
193. Lindheim SR, Duffy DM, Kojima T, Vijod MA, Stanczyk FZ and Lobo RA: The route of administration influences the effect of estrogen on insulin sensitivity in postmenopausal women. *Fertil Steril* 62:1176-1180, 1994.
194. Lobo RA, Pickar JH, Wild RA, Walsh B, Hirvonen E and the Menopause Study Group: Metabolic impact of adding medroxyprogesterone acetate to conjugated estrogen therapy in postmenopausal women. *Obstet Gynecol* 84:987-995, 1994.
195. Lobo RA and Speroff L: International consensus conference on postmenopausal hormone therapy and the cardiovascular system. *Fertil Steril* 62 (Suppl 2): 176-179S, 1994.
196. Lobo RA: Investigating the cause of hirsutism and acne in women. *Clin Chem* 41:12-13, 1995.
197. Wong IL, Morris RS, Chang L, Spahn M-A, Stanczyk FZ and Lobo RA: A prospective randomized trial comparing finasteride to spironolactone in the treatment of hirsute women. *J Clin Endocrinol Metab* 80:233-238, 1995.
198. Lupp P, Müller B, Jacob K, Kimmig R, Strowitzki T, Höss C, Weber MM, Engelhardt D and Lobo RA: Variations of steroid hormone metabolites in serum and urine in

- polycystic ovary syndrome after nafarelin stimulation: Evidence for an altered corticoid excretion. *J Clin Endocrinol Metab* 80:280-288, 1995.
199. Legro RS, Wong IL, Paulson RJ, Lobo RA and Sauer MV: Recipient's age does not adversely affect pregnancy outcome after oocyte donation. *Am J Obstet Gynecol* 172:96-100, 1995.
  200. Ditkoff EC, Fruzzetti F, Chang L, Stanczyk FZ and Lobo RA: The impact of estrogen on adrenal androgen sensitivity and secretion in polycystic ovary syndrome. *J Clin Endocrinol Metab* 80:603-607, 1995.
  201. Carmina E, Gentzschein E, Stanczyk FZ and Lobo RA: Substrate dependency of C<sub>19</sub> conjugates in hirsute hyperandrogenic women and the influence of adrenal androgen. *Hum Reprod* 10:299-303, 1995.
  202. Lindheim SR, Legro RS, Morris RS, Vijod MA, Lobo RA, Paulson RJ and Sauer MV: Altered responses to stress in women undergoing in-vitro fertilization and recipients of oocyte donation. *Hum Reprod* 10:320-323, 1995.
  203. Wong IL, Morris RS, Lobo RA, Paulson RJ and Sauer MV: Isolated polycystic morphology in ovum donors predicts response to ovarian stimulation. *Hum Reprod* 10:524-528, 1995.
  204. Sauer MV, Paulson RJ and Lobo RA: Triplet pregnancy in a 51-year-old woman after oocyte donation. *Am J Obstet Gynecol* 172:1044-1045, 1995.
  205. Koopersmith TB and Lobo RA: Insulin sensitivity is unaltered by the use of the Norplant<sup>(R)</sup> subdermal implant contraceptive. *Contraception* 51:197-200, 1995.
  206. Morris RS, Carmina E, Vijod MA, Stanczyk FZ and Lobo RA: Alterations in the sensitivity of serum insulin-like growth factor 1 and insulin-like growth factor binding protein-3 to octreotide in polycystic ovary syndrome. *Fertil Steril* 63:742-746, 1995.
  207. Duffy DM, Lindheim SR, Vijod MA, Chang L, Nakamura RM and Lobo RA: Low-dose growth hormone-releasing factor may enhance folliculogenesis in regularly menstruating women: A preliminary study. *Fertil Steril* 63:756-760, 1995.
  208. Legro RS, Muhleman DR, Comings DE, Lobo RA and Kovacs BW: A dopamine D<sub>3</sub> receptor genotype is associated with hyperandrogenic chronic anovulation and resistant to ovulation induction with clomiphene citrate. *Fertil Steril* 63:779-784, 1995.
  209. Legro RS, Wong IL, Paulson RJ, Lobo RA and Sauer MV: Multiple implantation following oocyte donation: A frequent but inefficient event. *Fertil Steril* 63:849-853, 1995.



210. Morris RS, Paulson RJ, Lindheim SR, Legro RS, Lobo RA and Sauer MV: Angiotensin converting enzyme inhibition reverses luteal phase steroid production in oocyte donors. *Fertil Steril* 63:854-858,1995.
211. Morris RS, Paulson RJ, Sauer MV, Lobo RA: Predictive value of serum oestradiol concentrations and oocyte number in severe ovarian hyperstimulation syndrome. *Hum Reprod* 10:811-814,1995.
212. Lobo RA: A disorder without identity: "HCA," "PCO," "PCOD," "PCOS," "SLS." What are we to call it? *Fertil Steril* 63:1158-1160,1995.
213. Carmina E, Gonzalez F, Chang L and Lobo RA: Reassessment of adrenal androgen secretion in women with polycystic ovary syndrome. *Obstet Gynecol* 85:971-976,1995.
214. Sauer MV, Paulson RJ, Francis MM, Macaso TM and Lobo RA: Pre-implantation adoption: Establishing pregnancy using donated oocytes and sperm. *Hum Reprod* 10:1419-1422,1995.
215. Sauer MV, Paulson RJ and Lobo RA: Pregnancy after 50 or more years of age: Outcomes of 22 consecutively established pregnancies from oocyte donation. *Fertil Steril* 64:111-115,1995.
216. Stanczyk FZ, Rosen GF, Ditkoff E, Vijod AG, Bernstein L and Lobo RA: Influence of estrogen on prostacyclin and thromboxane balance in postmenopausal women. *Menopause* 2:137-143,1995.
217. Carmina E, Stanczyk FZ, Gentschein E and Lobo RA: Time-dependent changes in serum  $3\alpha$ -androstenediol glucuronide correlate with hirsutism scores after ovarian suppression. *Gynecol Endocrinol* 9:215-220,1995.
218. Duffy DM, Legro RS, Chang L, Stanczyk FZ and Lobo RA: Metabolism of dihydrotestosterone to  $5\alpha$ -androstane- $3\alpha$ -17 $\beta$ -diol glucuronide is greater in the peripheral compartment than in the splanchnic compartment. *Fertil Steril* 64:736-739, 1995.
219. Carmina E, Stanczyk FZ, Morris RS, Lee PDK, Savjani G and Lobo RA: Altered regulation of insulin-like growth factor binding protein-1 in patients with polycystic ovary syndrome. *J Soc Gynecol Invest.* 2:743-747, 1995.
220. Morris RS, Wong IL, Hatch IE, Gentschein E, Paulson RJ, Lobo RA: Prorenin is elevated in polycystic ovary syndrome and may reflect hyperandrogenism. *Fertil Steril* 64:1099-1103,1995.
221. Morris RS, Wong IL, Do YS, Hsueh WA, Lobo RA, Sauer MV, Paulson RJ: The pathophysiology of ovarian hyperstimulation syndrome (OHSS). A proposal role of the ovarian derived prorenin to angiotensin cascade (ODPAC) [Review]. *Adv Exp Med Biol*

377:391-398, 1995.

222. Lobo RA: Benefits and risks of estrogen replacement therapy. *Am J Obstet Gynecol* 173:982-989, 1995.
223. Lobo RA: Polycystic ovary syndrome/hyperandrogenic chronic anovulation [Review]. *Adv Endocrinol Metab* 6:167-191, 1995.
224. Lobo RA: Estrogen replacement: The evolving role of alternative delivery systems. Introduction. *Am J Obstet Gynecol* 173:981, 1995.
225. Lindheim SR, Sauer MV, Francis MM, Macasos TM, Lobo RA and Paulson RJ: The significance of elevated early follicular phase follicle stimulating hormone (FSH) levels: Observations in unstimulated in vitro fertilization cycles. *J Assist Reprod Genet* 13:49-52, 1996.
226. Sauer MV, Paulson RJ, Lobo RA: Rare occurrence of ovarian hyperstimulation syndrome in oocyte donors. *Int J Gynecol Obstet* 52:259-262, 1996.
227. Lobo RA, Skinner JB, Lippman J and Cirillo SJ: Plasma lipids and desogestrel/ethinyl estradiol: A meta-analysis. *Fertil Steril* 65:1100-1109, 1996.
228. Lobo RA, Ettinger B, Hutchinson KA, Knopp RH, Lindsay R, Nachtigall LE, Santoro N and Studd J: Estrogen Replacement. The Evolving Role of Transdermal Delivery. *J Reprod Med* 41:781-796, No. 10 (Suppl.) 1996.
229. Lobo RA: Treatment of the postmenopausal woman: Basic and clinical aspects [Review]. *South African Medical Journal*, Spring 1996.
230. Wilcox JG, Stanczyk FZ, Morris RS, Gentzschein E and Lobo RA: Biologic effects of  $17\alpha$ -dihydroequilin sulfate. *Fertil Steril* 66:748-752, 1996.
231. Gonzalez F, Chang L, Horab T and Lobo RA: Evidence for heterogeneous etiologies of adrenal dysfunction in polycystic ovary syndrome. *Fertil Steril* 66:354-361, 1996.
232. Carmina E, Lo Dico G, Carollo F, Stanczyk FZ and Lobo RA: Serum IGF-1 and the binding proteins 1 and 3 in postmenopausal women and the effects of estrogen. *Menopause* 3:85-89, 1996.
233. Lobo RA: Therapeutic Controversy: Estrogen Replacement in Menopause. *J Clin Endocrinol Metab* 81:3829-3838, 1996.
234. Lindsay R, Bush TL, Grady D, Speroff L and Lobo RA: Therapeutic Controversy. Estrogen Replacement in Menopause. *J Clin Endocr Metab* 81:3829-3838, 1996.
235. Sauer MV, Paulson RJ and Lobo RA: Oocyte donation to women of advanced

- reproductive age: pregnancy results and obstetrical outcomes in patients 45 years and older. *Hum Reprod* 11:2540-2543, 1996.
236. Edwards RG, Lobo R and Bouchard P: Time to revolutionize ovarian stimulation. *Hum Reprod* 11:917-919, 1996.
  237. Lobo RA: ART reporting: The American view. *Hum Reprod* 11:1369-1370, 1996.
  238. Guess HA, Friedman GD, Sadler MC, Stanczyk FZ, Volgelman JH, Imperato-McGinley J, Lobo RA and Orentreich N:  $5\alpha$ -reductase activity and prostate cancer: A case-control study using stored sera. *Canc Epid Biomark & Prevent* 6:21-24, 1997.
  239. Paulson RJ, Sauer MV, Lobo RA: Potential enhancement of endometrial receptivity in cycles using controlled ovarian hyperstimulation with antiprogesterins: a hypothesis. *Fertil Steril* 67:321-325, 1997.
  240. Wilcox JG, Hatch IE, Gentzschein E, Stanczyk FZ, Lobo RA: Endothelin levels decrease after oral and nonoral estrogen in postmenopausal women with increased cardiovascular risk factors. *Fertil Steril* 67:273-277, 1997.
  241. Wilcox JG, Hwang J, Hodis HN, Sevanian A, Stanczyk FZ and Lobo RA: Cardioprotective effects of individual conjugated equine estrogens through their possible modulation of insulin resistance and oxidation of low-density lipoprotein. *Fertil Steril* 67:57-62, 1997.
  242. Price TM, Blauer KL, Hansen M, Stanczyk FZ and Lobo RA: Single dose pharmacokinetics of sublingual versus oral administration of micronized  $17\beta$ -estradiol. *Obstet Gynecol* 89:340-345, 1997.
  243. Edwards RG, Lobo RA and Bouchard P: Why delay the obvious need for milder forms of ovarian stimulation? *Hum Reprod* 12:399-401, 1997.
  244. Stanczyk FZ, Gentzschein E, Ary BA, Kojima T, Ziogas A and Lobo RA: Urinary progesterone and pregnanediol glucuronide: Use for monitoring progesterone treatment. *J Reprod Med* 42:216-222, 1997.
  245. Carmina E and Lobo RA: Gonadotrophin- releasing hormone agonist therapy for hirsutism is as effective as high dose cyproterone acetate but results in a longer remission. *Hum Reprod* 12:663-666, 1997.
  246. Paulson RJ, Hatch IE, Lobo RA, Sauer MV: Cumulative conception and live birth rates after oocyte donation: implications regarding endometrial receptivity. *Hum Reprod* 12:835-839, 1997.
  247. Carmina E, Wong L, Chang L, Paulson RJ, Sauer MV, Stanczyk FZ and Lobo RA:

- Endocrine abnormalities in ovulatory women with polycystic ovaries on ultrasound. *Hum Reprod* 12:905-909, 1997.
248. Sauer MV, Paulson RJ and Lobo RA: Comparing the clinical utility of GnRH antagonist to GnRH agonist in an oocyte donation program. *Gynecol Obstet Invest* 43:215-218, 1997.
  249. Lindheim SR, Sauer MV, Francis MM, Macaso T, Lobo R and Paulson RJ: The utility of a midcycle follicle-stimulating hormone boost in addition to human chorionic gonadotropin for timing of follicle aspiration in unstimulated in vitro fertilization cycles. *Gynecol Obstet Invest* 43:76-78, 1997.
  250. Koopersmith TB, Lindheim SR, Lobo RA, Paulson RJ and Sauer MV: Outcomes of high-order multiple implantations in women undergoing ovum donation. *J Matern-Fetal Med* 6:268-272, 1997.
  251. Vatten LJ, Ursin G, Ross RK, Stanczyk FZ, Lobo RA, Harvei S and Jellum E: Androgens in serum and the risk of prostate cancer: A nested case-control study from the Janus Serum Bank in Norway. *Canc Epidemiol Biomarkers Prev* 6:967-969, 1997.
  252. Lobo RA: New trends in transdermal HRT and aspects on climacteric psychology. *Europ Menopause J* 4:1-4, 1997.
  253. Lobo RA: Foreword. CME Activity. Progesterone use in reproductive and gynecologic endocrinology: Current and future perspectives. *Contemporary OB/GYN (Supplement)* 42:3, 1997.
  254. Carmina E and Lobo RA: The addition of dexamethasone to antiandrogen therapy for hirsutism prolongs the duration of remission. *Fertil Steril* 69:1075-1079, 1998.
  255. Pickar JH, Wild RA, Walsh B, Hirvonen E and Lobo RA: Effects of different hormone replacement regimens on postmenopausal women with abnormal lipid levels. *CLIMACTERIC* 1:26-32, 1998.
  256. Carmina E and Lobo RA: Adrenal hyperandrogenism in the pathophysiology of Polycystic Ovary Syndrome. *J Endocrinol Invest* 21:580-588, 1998.
  257. Lobo RA: The Perimenopause. *Clin Obstet Gynecol* 41:895-897, 1998.
  258. Lobo RA: Perimenopause [Foreword]. *Clin Obstet Gynecol* 41:894, 1998.
  259. Lobo RA (Program Chairman and Course Director). CME Activity. Natural Progesterone: Mechanisms, Effects, and Safety. *Contemp OB/GYN*, Sept. 1998.
  260. Lobo RA. Low dose therapy. *Contemp Ob/Gyn* 43 (Suppl. 5), May 1998.

261. Carmina E, Gonzalez F, Vidali A, Stanczyk FZ, Ferin M and Lobo RA: The contributions of estrogen and growth factors to increased adrenal androgen secretion in polycystic ovary syndrome. *Hum Reprod* 14:307-11, 1999.
262. Carmina, E and Lobo RA: Do hyperandrogenic women with normal menses have PCOS? *Fertil Steril* 71:319-22, 1999.
263. Fraser IS, Lobo RA: Update on Progestogen Therapy, a Journal Supplement Based on a Consensus Development Conference Sponsored by the College of Physicians and Surgeons of Columbia University, held on October 3 and 4, 1998, in San Francisco, California. *J Reprod Med* 44:139-140 (Suppl. #2), 1999.
264. Lobo RA. Progestogen Metabolism. *J Reprod Med* 44 (2 Suppl):148-152, 1999.
265. Gonzalez F, Chang L, Horab T, Stanczyk FZ, Crickard K, Lobo RA. Adrenal dynamic responses to physiologic and pharmacologic adrenocorticotrophic hormone stimulation before and after ovarian steroid modulation in women with polycystic ovary syndrome. *Fertil Steril* 71:439-44, 1999.
266. Carmina E, Lobo RA. Editorial. COMMENTARY. Polycystic ovary syndrome (PCOS) arguably the most common endocrinopathy is associated with significant morbidity in women. *J Clin Endocrinol Metab* 84:1897-9, 1999.
267. Lindsay R, Cosman F, Lobo RA, Walsh BW, Harris ST, Reagan JE, Liss CL, Melton ME, Byrnes CA. Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: A randomized, controlled clinical trial. *J Clin Endocrinol Metab* 84:3076-81, 1999.
268. Lobo RA. Commentary. Two-year prospective, randomized trial comparing an innovative twice-a-week progestin regimen with a continuous combined regimen as postmenopausal hormone therapy by Antonio Cano et al. *Fertil Steril* 71:129-136, 1999. JAMA Women's Health web site, 1999 ([www.amaassn.org/special/womh](http://www.amaassn.org/special/womh)).
269. Archer DF, Lobo RA, Land HF, and Pickar JH. A comparative study of transvaginal uterine ultrasound and endometrial biopsy for evaluating the endometrium of postmenopausal women taking hormone replacement therapy. *Menopause* 6:201-8, 1999.
270. Carmina E, Ferin M, and Lobo RA. Evidence that insulin and adrenal androgens participate in the regulation of serum leptin levels in women. *Fertil Steril* 72:926-31, 1999.
271. Legro RS, Blanche P, Krauss RM and Lobo RA. Alterations in low-density lipoprotein and high-density lipoprotein subclasses among Hispanic women with polycystic ovary syndrome: influence of insulin and genetic factors. *Fertil Steril* 72:990-5, 1999.
272. Birken, S, Santoro N, Maydelman Y, Galina MA, Kovalevskaya G, Lobo RA, Freeman

- EW, Warren M, McMahon D and O'Connor J. Differences in urinary excretion patterns of the hLH beta core fragment in premenopausal, perimenopausal and postmenopausal women. *Menopause* 6:290-8, 1999.
273. Lobo RA, Zacur HZ, Caubel P and Lane R. A novel pulsed regimen of norgestimate preserve the beneficial effects of 17 $\beta$ -estradiol on lipids and lipoprotein profiles. *Am J Obstet Gynecol* 182:41-49,2000.
  274. Lindheim S, Sauer MV, Carmina E, Chang PL, Zimmermann R, Lobo RA. Circulating leptin levels during ovulation induction: relation to adiposity and ovarian morphology. *Fertil Steril* 73:493-98, 2000.
  275. Lobo RA. Maximize the benefit of hormone replacement therapy. *J Reprod Med* 45: No.3/March 243-4,2000 (Suppl.).
  276. Chang P, Lindheim SR, Lowre C, Ferin M, Gonzalez F, Berglund L, Carmina E, Sauer MV, Lobo RA. Normal ovulatory women with polycystic ovaries have hyperandrogenic pituitary-ovarian responses to gonadotropin-releasing hormone-agonist testing. *J Clin Endocr Metab* 85:995-1000, 2000.
  277. Lobo RA, Carmina E. Perspective. The importance of diagnosing the polycystic ovary syndrome. *Ann Int Med* 132:989-93, 2000.
  278. Dunaif A, Utian WH, Brandenburg SL, Gerhard M, Lobo RA, Caren G, Solomon CG, Sowers JR. Effects of menopause and Estrogen Replacement Therapy or Hormone Replacement Therapy in Women with Diabetes Mellitus: Consensus Opinion of The North American Menopause Society. *Menopause* 7:87-95, 2000.
  279. Lobo RA, et al. Current Management of Recurrent Pregnancy Loss. Sponsored by the College of Physicians and Surgeons of Columbia University. *Contemp OB/GYN* (Suppl) February, 2000.
  280. Upmalis DH, Lobo RA, Bradley L, Warren M, Cone FL, Lamia CA. Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women: a multicenter, double-blind, randomized, placebo-controlled study. *Menopause* 7:236-42,2000.
  281. Zimmermann RC, Xiao E, Husami N, Sauer MV, Lobo RA, Kitajewski J, Ferin M. Short-term administration of antivascular endothelial growth factor antibody in the late follicular phase delays follicular development in the Rhesus monkey. *J Clin Endocrinol Metab* 86:768-72, 2001.
  282. Lobo RA. Priorities in polycystic ovary syndrome. *The Med J Australia* 174:554-555,2001.
  283. Lobo RA. CME Review Article. Androgens in postmenopausal women: production, possible role and replacement options. *Obstet Gynecol Survey* 56:361-376,2001.

284. Lobo RA, Whitehead MI. Is low-dose hormone replacement therapy for postmenopausal women efficacious and desirable? *Climacteric* 4:110-19,2001.
285. Lobo RA, Bush T, Carr BR, Picar JH. Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on plasma lipids and lipoproteins, coagulation factors, and carbohydrate metabolism. *Fertil Steril* 76:13-24,2001.
286. Lobo RA. Dietary Soy and cardiovascular disease risk. *Menopause* 8:303-4, 2001.
287. Lobo RA. Menopause: Approach to therapy. *Precis: Reproductive Endocrinology*, Second Edition. 2001.
288. Cha KY, Wirth DP and Lobo RA. Does prayer influence the success of in vitro fertilization embryo transfer (IVF-ET)? Report of a masked randomized trial. *J Reprod Med* 46:781,2001.
289. Carmina E, Lobo RA. Polycystic ovaries in hirsute women with normal menses. *Am J Med* 111:602, 2001.
290. Lobo RA. Progestogens: New Approaches. *The Female Patient (Suppl.)* October 2001:19-22.
291. Lobo RA. Recent findings in cardiovascular disease. *The Female Patient (Suppl.)* October 2001:3-4.
292. Hodis HN, Mack WJ, Lobo RA, Shoupe D, Sevanian A, Mahrer PR, Selzer RH, Liu C-R, Liu C-H, Azen SP. Estrogen in the prevention of atherosclerosis: A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 135:939-53, 2002.
293. Hodis, HN, Mack WJ, Lobo RA. Postmenopausal hormone replacement therapy as antiatherosclerotic therapy. *Curr Atheroscler Rep.* 4:52-8, 2002.
294. Pinn VW, Lobo RA. Preface. Androgen Insufficiency in Women: The Princeton Conference. Special Supplement. *Fertil Steril.* 77:#4, Suppl.4, S1,2002.
295. Bachmann G, Bancroft J, Braunstein G, Burger, H, Davis S, Dennerstein L, Goldstein I, Guay A, Leiblum S, Lobo RA, Notelovitz M, Rosen R, Sarrel P, Sherwin B, Simon J, Simpson E, Shifren J, Spark R, Traish A. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertil Steril* 77:660-665, 2002.
296. Carmina E, Godwin AJ, Stanczyk FZ, Lippman JS, Lobo RA. Serum androsterone glucuronide reflects inflammatory lesions in women with adult acne. *J Endocrinol Invest.* 25:765-68, 2002.

297. Hodis HN, Mack WJ, Lobo RA. Antiatherosclerosis interventions in women. *Am J Cardiol* 90:17F-21F, 2002.
298. Carmina E, Lobo RA. A comparison of the relative efficacy of antiandrogens for the treatment of acne in hyperandrogenic women. *Clin Endocrinology* 57:231-234, 2002.
299. Lobo RA. Editorial. Menopausal medicine. *Best Pract Res Clin Obstet Gynaecol* 16(3):ix-xii, 2002.
300. Grimes DA, Lobo RA. Perspectives on the Women's Health Initiative trial of hormone replacement therapy. *Obstet Gynecol* 100:1344-53, 2002.
301. Dunaif A, Lobo RA. Toward optimal health: the experts discuss polycystic ovary syndrome. *J Womens Health Gend Based Med* 11:579-84, 2002.
302. Carmina E, Lobo RA. Treatment of hyperandrogenic alopecia in women. *Fertil Steril*. 79:91-95, 2003.
303. Lobo RA. News about the Journal of the Society for Gynecologic Investigation. *J Soc Gynecol Investig* 10:1, 2003.
304. Mack WJ, Hameed AB, Xiang M, Roy S, Slater CC, Stanczyk FZ, Lobo RA, Liu C-r, Liu Ci, Hodis, HN. Does elevated body mass modify the influence of postmenopausal estrogen replacement on atherosclerosis progression: results from the estrogen in the prevention of atherosclerosis trial. *Atherosclerosis* 00 (2003) 1-8 (in press).
305. Lobo RA, Rosen RC, Yang H-M, Block BA, Gerritsen R, Hoop Va der. Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. *Fertil Steril* (in press, 2003).
306. Lobo RA. Editorial response to the article entitled "Androgen excess is the key element in polycystic ovary syndrome by Ricardo Azziz. *Fertil Steril* 2003 (in press).
307. Lobo RA, Archer DF, Ettinger B, Gambrell RD, Liu JH, Sitruk-Ware R, Stanczyk FZ, Wagner JD. Role of progestogen in hormone therapy for postmenopausal women: position statement of The North American Menopause Society. *Menopause* 2003 (in press).
308. Carmina E, Longo A, Lobo RA. Does ovarian blood flow distinguish between ovulatory and anovulatory patients with polycystic ovary syndrome? *Am J Obstet Gynecol* (submitted 2003).
309. Carmina, E, Legro R, Stamets J, Lowell J, Lobo RA. The influence of diet on obesity and dyslipidemia in polycystic ovary syndrome. Submitted to *Hum Reprod* (2003).



310. Silfen ME, Denburg MR, Manibo AM, Lobo RA, Jaffe R, Ferin M, Levine LS, Oberfield SE. Early endocrine, metabolic, and sonographic characteristics of polycystic ovarian syndrome (PCOS): Comparison between non-obese and obese adolescents.
311. Carmina E, Lobo RA. Effect of the estrogen dose in the treatment of hirsutism using cyproterone acetate. Submitted to Hum Reprod (2003).
312. Mosca, L, Lobo RA. Management of dyslipidemia for the prevention of heart disease in women. A Clinical Guide for Obstetricians and Gynecologists. Submitted to Am College of Obstet Gynecol Monograph (2003).
313. Hodis HN, Mack WJ, Lobo RA, Shoupe D, Mahrer PR, Faxon DP, et al. Women's estrogen-progestin lipid lowering hormone atherosclerosis regression trial (WELL-HART): A randomized trial. Submitted to N Engl J Med (2003).

## Chapters in Books:

1. Lahteenmaki P, Lobo RA, Marrs RP, Gibbons WE, Nakamura RM and diZerega GS: Granulosa cells heterogeneity in women treated with clomiphene and human chorionic gonadotropin. In: Greenwald G and Terranova P (eds), *Proceedings of the IV Ovarian Workshop*, pp. 55-60, 1982. Raven Press, New York, New York.
2. Lobo RA: Androgen excess: Differential diagnosis. In: Mishell DR Jr and Brenner PF (eds), *Management of Common Problems in Obstetrics and Gynecology*, pp. 371-375, 1983. Medical Economics Company, Inc., Oradell, New Jersey.
3. Lobo RA: Androgen excess: Evaluation. In: Mishell DR Jr and Brenner PF (eds), *Management of Common Problems in Obstetrics and Gynecology*, pp. 376-378, 1983. Medical Economics, Inc., Oradell, New Jersey.
4. Lobo RA: Management of hirsutism. In: Mishell DR Jr and Brenner PF (eds), *Management of Common Problems in Obstetrics and Gynecology*, pp. 379-382, 1983. Medical Economics Company, Inc., Oradell, New Jersey.
5. Lobo RA: Adrenal gland reproduction. In: Garcia C-R, Mastroianni L Jr, Amelar RD and Dubin L (eds), *Current Therapy of Infertility 1984-1985*, pp. 46-50, 1984. B.C. Decker, Inc., Toronto, Ontario, Canada.
6. Lobo RA: The role of the adrenal in polycystic ovary syndrome. In: Speroff L (ed), *Seminars in Reproductive Endocrinology*, Volume 2, pp. 251-262, 1984. Thieme-Stratton, Inc., New York, New York.
7. Lobo RA: Androgen excess and the infertile female. In: Besch PK, Goldzieher JW and Gibbons WE (eds), *The Biochemistry of the Reproductive Years*, pp. 119-136, 1984. Kingsport Press, Kingsport, Tennessee.
8. Lobo R and Horton R: Hirsutism. In: Krieger DT and Bardin CW (eds), *Current Therapy in Endocrinology and Metabolism*, pp. 131-134, 1985. B.C. Decker, Inc., Toronto, Ontario, Canada.
9. Lobo RA: Disturbances of androgen secretion and metabolism in polycystic ovary syndrome. In: Jacobs HS (ed), *Reproductive Endocrinology, Clinics in Obstetrics and Gynaecology*, Volume 12, pp. 633-647, 1985. W.B. Saunders Ltd., London, England.
10. Hoffman DI, Lobo RA and Mishell DR Jr: Treatment of dysfunctional uterine bleeding. In: Baird DT and Michie EA (eds), *Mechanism of Menstrual Bleeding*, pp. 253-261, 1985. Raven Press, New York, New York.
11. Lobo RA: "Idiopathic hirsutism" - Fact or fiction? In: Speroff L (ed), *Seminars in Reproductive Endocrinology*, Vol 4, pp. 179-187, 1986. Thieme Inc., New York, NY.

12. Horton R and Lobo R: Peripheral androgens and the role of androstanediol glucuronide. In: Horton R and Lobo RA (eds), Androgen Metabolism in Hirsute and Normal Females, Clinics in Endocrinology and Metabolism, Volume 15, pp. 293-306, 1986. W.B. Saunders Company, Ltd., London, England.
13. Kletzky OA and Lobo RA: Reproductive Neuroendocrinology. In: Mishell DR Jr and Davajan V (eds), Infertility, Contraception and Reproductive Endocrinology, Second Edition, pp. 3-29, 1987. Medical Economics Company, Inc., Oradell, New Jersey.
14. Goebelsmann U and Lobo RA: Androgen excess. In: Mishell DR Jr and Davajan V (eds), Infertility, Contraception and Reproductive Endocrinology. Second Edition, pp. 303-317, 1987. Medical Economics Company, Inc., Oradell, New Jersey.
15. Lobo RA: Polycystic ovary syndrome. In: Mishell DR Jr and Davajan V (eds), Infertility, Contraception and Reproductive Endocrinology, Second Edition, pp. 319-336, 1987. Medical Economics Company, Inc., Oradell, New Jersey.
16. March CM, Hoffman DI and Lobo RA: Dysfunctional uterine bleeding. In: Mishell DR Jr and Davajana V (eds), Infertility, Contraception and Reproductive Endocrinology, Second Edition, pp. 337-351, 1987. Medical Economics Company, Inc., Oradell, New Jersey.
17. Lobo RA and Kletzky OA: Dynamics of hormone testing. In: Mishell DR Jr and Davajan V (eds), Infertility, Contraception and Reproductive Endocrinology, Second Edition, pp. 365-377, 1987. Medical Economics Company, Inc., Oradell, New Jersey.
18. Lobo RA: Prevention of postmenopausal osteoporosis. In: Mishell DR Jr (ed), Menopause: Physiology and Pharmacology, pp. 165-186, 1987. Year Book Medical Publishers, Inc., Chicago, IL.
19. Baranes RB and Lobo RA: Pharmacology of estrogens. In: Mishell DR Jr (ed), Menopause: Physiology and Pharmacology, pp. 301-315, 1987. Year Book Medical Publishers, Inc., Chicago, IL.
20. Lobo RA and Horton R: Hirsutism. In: Bayless TM, Brain MC and Cherniack RM (eds), Current Therapy in Internal Medicine- 2, pp. 506-508, 1987. B.C. Decker, Inc., Toronto, Ontario, Canada.
21. Lobo RA, Hirsutism. In: Sciarra JJ, Speroff L and Simpson JL (eds), Gynecology and Obstetrics, Volume 5, pp. 1-15, 1987. Reproductive Endocrinology, Infertility and Genetics. J.B. Lippincott Company, Philadelphia, Pennsylvania.

22. Lobo RA: Absorption and metabolic effects of different types of estrogens and progestogens. *In: Gambrell RD Jr (ed), The Menopause, Clinics in Obstetrics and Gynecology of North America, Vol. 14:143-167, 1987. W.B. Saunders Company, Philadelphia, PA.*
23. Barnes RB and Lobo RA: Endogenous opioids in polycystic ovary syndrome. *In: Speroff L (ed), Seminars in Reproductive Endocrinology, Vol. 5, pp. 185-189, 1987. Thieme Medical Publishers, Inc., New York, NY.*
24. Shoupe D and Lobo RA: Endogenous opioids in the menopause. *In: Speroff L (ed), Seminars in Reproductive Endocrinology, Volume 5, pp. 199-206, 1987. Thieme Medical Publishers, Inc., New York, NY.*
25. Lobo RA: Androgen excess and the infertile woman. *In: Kempers RD (ed), The Infertile Woman, Clinics in Obstetrics and Gynecology of North America, Volume 14, pp. 955-977, 1987. W.B. Saunders Company, Philadelphia, PA.*
26. Lobo RA: Prolactin secretion in polycystic ovary syndrome. *In: Blackwell RE and Chang RJ (eds), Prolactin-Related Disorders, pp. 137-149, 1987. Macmillan Healthcare Information, Inc., Florham Park, New Jersey.*
27. Lobo RA: Effects of oestrogens and progestogens on the cardiovascular system in post-menopausal women. *In: Zichella L, Whitehead MI and van Keep PA (eds), The Climacteric and Beyond, pp. 95-107, 1987. The Parthenon Publishing Group Ltd, Lancaster, England.*
28. Lobo RA: Polycystic ovary syndrome and hirsutism. *In: Imura H, Shizume K and Yoshida S (eds), Progress in Endocrinology 1988, Volume 2, pp. 1467-1472, 1988. Elsevier Science Publishers BV, Amsterdam, The Netherlands.*
29. Lobo RA: The menopause. *In: Rakel RE (ed), Conn's Current Therapy, Fortieth Edition, pp. 929-930, 1988. W.B. Saunders Company, Philadelphia, PA.*
30. Lobo RA: Androgen excess: Differential diagnosis. *In: Mishell DR Jr. and Brenner PF (eds), Management of Common Problems in Obstetrics and Gynecology, Second Edition, pp. 495-500, 1988. Medical Economics Company, Inc., Oradell, New Jersey.*
31. Lobo RA: Androgen excess: Evaluation. *In: Mishell DR Jr and Brenner PF (eds), Management of Common Problems in Obstetrics and Gynecology, Second Edition, pp. 501-504, 1988. Medical Economics Company, Inc., Oradell, New Jersey.*
32. Lobo RA: Management of hirsutism. *In: Mishell DR Jr. and Brenner PF (eds), Management of Common Problems in Obstetrics and Gynecology, Second Edition, pp. 505-509, 1988. Medical Economics Company, Inc., Oradell, New Jersey.*
33. Lob RA: Therapy of polycystic ovary syndrome. *In: Mishell DR Jr and Brenner PF*

- (eds), Management of Common Problems in Obstetrics and Gynecology, Second Edition, pp. 510-514, 1988. Medical Economics Company, Inc., Oradell, New Jersey.
34. Lobo RA: The role of neurotransmitters and opioids in polycystic ovarian syndrome. In: Mahajan DK (ed), Polycystic disease, Endocrinology and Metabolism Clinics of North America, pp. 667-683, 1988. W.B. Saunders Company, Philadelphia, PA.
  35. Lobo RA: Endocrine therapy of hyperandrogenism. In: Barbieri RL and Schiff I (eds), Reproductive Endocrine Therapeutics, pp. 101-126, 1988. Alan R. Liss, Inc., New York, NY.
  36. Lobo RA: Functional variations of the female genital tract. In: Wren BG and Lobo RA (eds), Handbook of Obstetrics and Gynaecology, Third Edition, pp. 299-322, 1989. Chapman and Hall Ltd., London, England.
  37. Lobo RA: Androgen excess in women: The enigma of the hirsute female. In: Soules MR (ed), Controversies in Reproductive Endocrinology and Infertility, pp. 59-77, 1989. Elsevier Science Publishing Company, Inc., New York, New York.
  38. Lobo RA: Cardiovascular disease, menopause, and the influence of hormonal replacement therapy. In: Hammond CB, Haseltine FP and Schiff I (eds), Menopause: Evaluation, Treatment and Health Concern, pp. 313-332, 1989. Alan R. Liss, Inc., New York, New York.
  39. Lobo RA: Hirsutism, alopecia, and acne. In: Becker KL and Rebar RW (eds), Principles and Practice of Endocrinology and Metabolism, pp. 834-848, 1990. J.B. Lippincott Company, Philadelphia, Pennsylvania.
  40. Lobo RA: Androgen excess of adrenal origin. In: Quilligan EJ and Zuspan FP (eds), Current Therapy in Obstetrics and Gynecology, Third Edition, pp. 3-7, 1990. W.B. Saunders Company, Philadelphia, Pennsylvania.
  41. Lobo RA: Estrogen and cardiovascular disease. In: Flint M, Kronenberg F and Utian W (eds), Multidisciplinary Perspectives on Menopause, Volume 592, pp. 286-294, 1990. Annals of the New York Academy of Sciences, New York, New York.
  42. Cassidenti DL and Lobo RA: Ovulatory disturbances in the hyperandrogenic woman. In: Diamond MP, DeCherney AH and Yee B (eds), Ovulation Induction, Infertility and Reproductive Medicine Clinics of North America, pp. 101-119, 1990. W.B. Saunders Company, Philadelphia, Pennsylvania.
  43. Kletzky OA and Lobo RA: Reproductive neuroendocrinology, In: Mishell DR Jr, Davajan V and Lobo RA (eds), Infertility, Contraception and Reproductive Endocrinology, Third Edition, pp. 3-33, 1991. Blackwell Scientific Publications, Cambridge, Massachusetts.

- Infertility, Contraception, and Reproductive Endocrinology, Fourth Edition. R.A. Lobo, D. R. Paulson and D. Shoupe (eds). Blackwell Scientific Publications, Malden, Massachusetts 1997, pp. 363-383.
76. Lobo R.A. and Carmina E. Androgen Excess. In: Mishell's Textbook of Infertility, Contraception, and Reproductive Endocrinology. Fourth Edition. R.A. Lobo, D. R. Paulson and D. Shoupe (eds). Blackwell Scientific Publications, Malden, Massachusetts 1997, pp. 342-362.
  77. Carmina E. and Lobo RA: Dynamic Tests for Hormone Evaluation. In: Mishell's Textbook of Contraception, and Reproductive Endocrinology. Fourth Edition. R.A. Lobo, D. R. Paulson and D. Shoupe (eds). Blackwell Scientific Publications, Malden, Massachusetts 1997, pp. 471-483.
  78. Lobo RA: The Postmenopausal State and Estrogen Deficiency. In: Estrogens and Anti-estrogens: Basic and Clinical Aspects. Robert Lindsay, David W. Dempster, and V. Craig Jordan (eds). Lippincott-Raven Publishers 1997, Chapter 6, pp. 63-72.
  79. Lobo RA: What is the Perimenopause? Serono Symposia USA, Inc. In: Perimenopause: R.A. Lobo (Ed), Springer-Verlag New York 1997, pp 1-3.
  80. Lobo RA: Hirsutism and Virilism. In: Carr DR and Blackwell RE (eds), Textbook of Reproductive Medicine: Second Edition, 1998. Appleton & Lange, Norwalk, Connecticut, Chapter 20, 405-423.
  81. Lobo RA: Hirsutism and Virilization. In: Precis- an update in obstetrics and gynecology. Reproductive Endocrinology. The American College of Obstetricians and Gynecologist Women's Health Care Physicians 1998, pp 48-50.
  82. Lobo RA: Estrogen Replacement Therapy. In: Knobil E and Neill JD (eds). Encyclopedia of Reproduction, Vol. 2. 1998. Academic Press, San Diego, CA, pp 101-108.
  83. Lobo RA: Designer estrogens: clinical aspects. In: R.D. Kempers, J. Cohen, A.F. Haney and J.B. Younger. Fertility and Reproductive Medicine. Proceedings of the XVI World Congress on Fertility and Sterility, San Francisco, 4-9 October, 1998. pp 555-562. Elsevier, Amsterdam-New York-Oxford.
  84. Lobo RA: Polycystic Ovary Syndrome (PCOS). In: Fraser IS, Jansen RPS, Lobo RA and Whitehead MI (eds). Estrogens and Progestogens in Clinical Practice. Churchill-Livingstone, London, 1998, pp 405-417.
  85. Lobo RA: Primary and Secondary Amenorrhea. In: Fraser IS, Jansen RPS, Lobo RA and Whitehead MI (eds). Estrogens and Progestogens in Clinical Practice. Churchill-Livingstone, London, 1998, pp 357-363.

86. Lobo RA: Assisted Reproductive Technologies. In: Fraser IS, Jansen RPS, Lobo RA and Whitehead MI (eds). Estrogens and Progestogens in Clinical Practice. Churchill-Livingstone, London, 1998, pp 507-520.
87. Lobo RA: Estrogen Replacement Therapy. Encyclopedia of Reproduction Vol. 2, 1999. Academic Press, San Diego, California, pp 101-108.
88. Lobo RA: Menopause. In: Goldman L, Bennett JC, et al: Cecil Textbook of Medicine, 21<sup>st</sup> edition. W.B. Saunders Company, Philadelphia, PA. 1999.
89. Lobo RA. The Perimenopause. Chapter 5. In: Lobo RA (ed). Treatment of the Postmenopausal Woman, 2<sup>nd</sup> Edition. Lippincott Williams & Wilkins, New York, NY, 1999.
90. Lobo RA. Hormonal Replacement: Routes of Administration. Chapter 13. In: Lobo RA (ed). Treatment of the Postmenopausal Woman, 2<sup>nd</sup> Edition. Lippincott Williams & Wilkins, New York, NY, 1999.
91. Lobo RA. Treatment of the Postmenopausal Woman: Where We Are Today. Chapter 62. In: Lobo RA (ed). Treatment of the Postmenopausal Woman, 2<sup>nd</sup> Edition. Lippincott Williams & Wilkins, New York, New York. 1999.
92. Lobo RA. Prevalence and Clinical Impact of PCOS. Update for the online version of McGraw-Hill's Harrison's Principles of Internal Medicine, 14e, Anthony Fauci et al., (eds), 1999.
93. Lobo RA. Progestogens. Chapter 30, pp. 429. Menopause: Biology and Pathobiology. In: Lobo RA, Marcus R & Kelsey J (Eds.). The Academic Press, San Diego, CA. 2000.
94. Carmina E, Lobo RA. Hirsutism, Alopecia, and Acne. Chapter 101. In: Becker K.J. Principles and Practice of Endocrinology and Metabolism, Third Edition. J.B. Lippincott Williams & Wilkins, Philadelphia, 2001.
95. Lobo RA. Treatment of hyperandrogenism. Ch. 23, pp 327-348. In: Chang J, Heindel J Dunaif A. Polycystic Ovary Syndrome. Marcel-Dekker, New York, NY 2002.
96. Lobo RA. Menopause. In: Cecil Textbook of Medicine 22<sup>nd</sup> edition. Edited by Lee Goldman and Dennis Ausiello. Ch. 256. W.B. Saunders, Philadelphia, PA. 2002.
97. Lobo RA. Recent findings in cardiovascular disease. Chapter 14. HRT and Cardiovascular Disease: A New Approach. In: Lobo RA, Crosignani PG, Paoletti R and Bruschi F (Eds). Kluwer Academic Publishers, Dordrecht/Boston/London, 2002, pp. 137-141.
98. Lobo RA. Progestogens: New Approaches. In: Lobo RA, Crosignani PG, Paoletti R and Bruschi F (Eds). Kluwer Academic Publishers, Dordrecht/Boston/London, 2002, pp.

167-173.

- 99 Samsioe G, Doren M, Lobo RA (eds). In: **Menopause. Rapid Reference to Menopause.** Mosby, London 2002.



### Book Editorships:

1. Horton R and Lobo RA: Androgen metabolism in normal and hirsute females. In: Clinics in Endocrinology and Metabolism, Volume 15:2, 1986. W.B. Saunders Company, Ltd., London, England.
2. Lobo RA: Role of opioid peptides in reproductive endocrinology. In: Seminars in Reproductive Endocrinology, Volume 5:2, 1987. Thieme Medical Publishers, Inc., New York, N.Y.
3. Wren BG, and Lobo RA: Handbook of Obstetrics and Gynaecology, Third Edition, 1989. Chapman and Hall Ltd., London, England.
4. Lobo RA and Whitehead MI: Consensus Development Conference on Progestogens. International Proceedings Journal, Volume 1, Number 1, 1989. Worldwide Medical Group, New York, N.Y.
5. Mishell DR Jr, Paulsen CA and Lobo RA: 1989 Year Book of Infertility. Year Book Medical Publishers, Chicago, Illinois.
6. Mishell DR Jr, Paulen CA and Lobo RA: 1990 Year Book of Infertility. Mosby-Year Book, Inc., Chicago, Illinois.
7. Mishell DR Jr, Davajan V and Lobo RA: Infertility, Contraception and Reproductive Endocrinology, Third Edition, 1991. Blackwell Scientific Publication, Cambridge, Massachusetts.
8. Mishell DR Jr, Paulsen CA and Lobo RA: 1991 Year Book of Infertility. Mosby-Year Book, Inc., Chicago, Illinois.
9. Lobo RA and Naftolin F: Progesterone in Hormonal Replacement Therapy, 1992. The Parthenon Publishing Group Inc., Park Ridge, New Jersey.
10. Mishell DR Jr, Paulsen CA and Lobo RA: 1992 Year Book of Infertility. Mosby-Year Book, Inc., Chicago, Illinois.
11. Mishell DR Jr, Sokol RZ and Lobo RA: 1993 Year Book of Infertility. Mosby-Year Book, Inc., Chicago, Illinois.
12. Lobo RA: Treatment of the Postmenopausal Woman: Basic and Clinical Aspects, 1994. Raven Press, New York, NY.
13. Mishell DR Jr, Sokol RZ and Lobo RA: 1994 Year Book of Infertility. Mosby-Year Book, Inc., Chicago, Illinois.

14. Lobo RA and Speroff L: Menopausal Medicine. 1993-1995. The American Fertility Society, Birmingham, Alabama.
15. Mishell DR Jr, Sokol RZ and Lobo RA:1995 Year Book of Infertility. Mosby-Year Book, Inc., Chicago, Illinois.
16. Mishell DR Jr, Lobo RA and Sokol RZ:1996 Year Book of Infertility and Reproductive Endocrinology. Mosby-Year Book, Inc., Chicago, Illinois.
17. Lobo RA, Mishell DR Jr, Paulson RJ and Shoupe D:1997.Mishell's Textbook of Infertility, Contraception and Reproductive Endocrinology, Fourth Edition. Blackwell Scientific Publication, Malden, Massachusetts.
18. Lobo RA: Perimenopause. Serono Symposia USA, Springer-Verlag, New York, Inc. 1997.
19. Pitkin, RM, Scott JR (Eds), Duff P and Lobo, RA (Guest Eds): Clinical Obstetrics & Gynecology, Vol. 41, # 4, 1998, Lippincott Williams & Wilkins, Philadelphia, PA.
20. Fraser I, Jansen RPS, Lobo RA and Whitehead MI: Estrogens and Progestogens in Clinical Practice. Churchill Livingstone, London, 1998.
21. Lobo RA. Treatment of the Postmenopausal Woman, 2<sup>nd</sup> Edition. Lippincott Williams & Wilkins, New York, NY 1999.
22. Lobo RA, Marcus R, Kelsey J. Menopause: Biology and Pathobiology. The Academic Press, San Diego, CA, 2000.
23. Lobo RA. Menopausal Medicine. Guest Editor. Bailliere's Best Practice & Research. Clinical Obstetrics and Gynaecology. In: S. Arulkumaran (Ed). Vol. 16 #3, June 2002.
24. Lobo RA, Crosignani PG, Paoletti R, Bruschi F. Women's Health and Menopause – New Strategies Improved Quality of Life. Vol. 17 Medical Science Symposia Series. Kluwer Academic Publishers, Dordrecht/Boston/London, 2002.

## EDUCATIONAL SERVICE

1. Lobo RA, Notelovitz M. Estrogen Replacement: The Evolving Role of Transdermal Delivery. Symposium in print, CME activity, October 1995.
2. Lobo RA. Genetic Control of Gametogenesis. Special Report: Women's Reproductive Health. Biomedical Frontiers, Advances in Science, Technology, and Medicine at Columbia Presbyterian Medical Center Vol. 5, Issue 1, Fall 1997.
3. Lobo RA. Foreword. CME Activity. Progesterone use in reproductive and gynecologic endocrinology: Current and future perspectives. A Supplement to Contemporary OB/GYN 42 #10 October 1997.
4. Lobo RA. Appraisal of the protective therapeutic effects of transdermal hormone replacement therapy. Symposium in Copenhagen, August 1997, on "New Trends in Transdermal HRT and Aspects on Climacteric Psychology.
5. Lobo RA.(Moderator). Polycystic Ovary Syndrome. An educational service of The American College of Obstetricians and Gynecologists. ACOG Update Vol. 24, July 1998.
6. Lobo RA, Mishell D, Speroff L. New Approaches to Addressing Women's Health Issues. Scientific Forum organized by Parke-Davis Women's Healthcare, Big Sky, Montana, August 20-23, 1998.
7. Lobo RA (Program Chairman and Course Director). CME Activity. Natural Progesterone: Mechanisms, Effects, and Safety. Contemporary OB/GYN (Suppl), Sept. 1998.
8. Lobo RA: Future directions in the treatment of hyperandrogenic anovulation. ACCME Update in Obstetrics and Gynecology/CLIER, October 2-3, 1998, Chicago, Illinois.
9. Lobo RA: Estrogens and antiestrogens for postmenopausal women. ACCME Update in Obstetrics and Gynecology /CLIER, October 2-3, 1998, Chicago, Illinois.
10. Lobo RA: Hirsutism and Virilization. *Precis*, Reproductive Endocrinology: an update in obstetrics and gynecology. The American College of Obstetricians and Gynecologists, Danvers, MA, 1998.
11. Adashi EY, Bates W, Berenson AB, Blackwell RE, Bronson RA, Carr BR, Carson SA, Dawood MY, Diamond MP, Dodson WC, Lobo RA et al (contributors). *Precis* an update in obstetrics and gynecology. Reproductive Endocrinology. In:Holzman GB, Rinehart RD, Moghissi KS (eds). 1998.

12. Lobo RA: The risks and benefits of hormone replacement therapy (HRT). Presented at The 53<sup>rd</sup> Annual Assembly of Southern California on February 3-7, 1999 in Los Angeles. Obstetrical and Gynecological Assembly of Southern California, 1999.
13. Lobo RA: The role of SERMs in women's health. Presented at The 53<sup>rd</sup> Annual Assembly of Southern California on February 3-7, 1999 in Los Angeles. Obstetrical and Gynecological Assembly of Southern California, 1999.
14. Lobo RA: Is there a new way to treat PCOS? Presented at The 53<sup>rd</sup> Annual Assembly of Southern California on February 3-7, 1999 in Los Angeles. Obstetrical and Gynecological Assembly of Southern California, 1999.
15. Lobo RA: What is new in ovulation induction? Presented at The 53<sup>rd</sup> Annual Assembly of Southern California on February 3-7, 1999 in Los Angeles. Obstetrical and Gynecological Assembly of Southern California, 1999.
16. ART: Where we are today. Presented at The 53<sup>rd</sup> Annual Assembly of Southern California on February 3-7, 1999 in Los Angeles. Obstetrical and Gynecological Assembly of Southern California, 1999.
17. Lobo, RA. Commentary: Cano et al: Two-year prospective, randomized trial comparing an innovative twice-a-week progestin regimen with a continuous combined regimen as postmenopausal hormone therapy. *Fertil Steril* 1999;71:129-136. Library of Women's Health Web Site. JAMA Women's Health Web Site 1999. ([www.amaassn.org/special/womh](http://www.amaassn.org/special/womh)).
18. Lobo RA. Fertility issues in PCOS: An overview. Syllabi for PCOS Course during the ASRM Conjoint Annual Meeting of the American Society for Reproductive Medicine and the Canadian Fertility and Andrology Society. ASRM/CFAS 1999, Toronto, Canada.
19. Lobo RA, Steroidogenesis in PCOS. Syllabi for PCOS Course during the ASRM Conjoint Annual Meeting of the American Society for Reproductive Medicine and the Canadian Fertility and Andrology Society. ASRM/CFAS 1999, Toronto, Canada.
20. Lobo RA. Diagnostic and follow up studies (GYN). Syllabi for PCOS Course during the ASRM Conjoint Annual Meeting of the American Society for Reproductive Medicine and the Canadian Fertility and Andrology Society. ASRM/CFAS 1999, Toronto, Canada.
21. Lobo RA and Fraser IS. Introduction. Update on Progestogen Therapy: Endometrial Protection Vol. 2, 1999. A CME monograph highlighting presentations from an educational symposium held during a Consensus Development conference October 1998. MPE Communications, The Healthcare Resource, 1999.

22. Lobo RA and Fraser IS. Introduction. Dr. Thomas B. Clarkson's monograph entitled "Update on Progestogen Therapy: Cardiovascular Considerations." MPE Communications, The Healthcare Resources, 1999.
23. Rogerio A. Lobo. Menopause Management for the Millennium. Valid for CME until December 13, 2000. <http://www.medscape.com/Medscape/WomensHealth/ClinicalMagmt/CM.v01/public/index.CM.v01.hln>.
24. Lobo RA. Clinical Management Module/Menopause. Medscape Women's Health Website, 2000.
25. Lobo RA (Program Chair), Branch DW, Reindollar RH, Carson SA (Panel) CME Activity. Current Management of Recurrent Pregnancy Loss. Contemp OB/GYN (Suppl.), February 2000.
26. Lobo RA. Hormone Replacement Therapy in the New Millennium. *The State of HRT in the New Millennium - Estrogen Deficiency and the Menopause -Home Study Program* sponsored by Wyeth-Ayerst Global Pharmaceuticals and Dowden Health Media Inc., 2000.
27. Lobo, RA HRT Casebook 1- *II-Bleeding Patterns and Adherence*. Therapeutic options when considering the impact of progestogens on cardiovascular risk factors. A CME Monograph. R.A. Lobo (editor). Sponsored by the College of Physicians and Surgeons of Columbia University, New York, NY. MPE Communications, Fair Lawn, New Jersey, Solvay Pharmaceuticals Inc., 2001.
28. Lobo RA. APGO educational module, "Improving Quality of Life During Menopause: The Role for Hormone Replacement Therapy." Current Therapeutics Inc., Beachwood, OH. 2001.
25. Lobo RA. Approach to therapy. *Precis: Reproductive Endocrinology*, Second Edition. 2002.
26. Barbieri RL, Lobo RA, Walsh BW, Santoro NF (Editorial Board). Improving quality of Life During Menopause. The Role of Hormone Replacement Therapy. Association of Professors of Gynecology and Obstetrics (APGO) Educational Series on Women's Health Issues, Current Therapeutics Inc., Beachwood, OH, 2002.
27. Lobo RA, et al. Female sexuality and hormone replacement therapy. A Focus on Androgen Insufficiency. CME Monograph based on Proceedings of the 4<sup>th</sup> Task Force on Female Sexuality held in New York City in February 2002. Sponsored by Medical Education Resources and is supported by an unrestricted educational grant from Solvay Pharmaceuticals.
28. Lobo RA. HRT and Menopausal Health. Clinical Implications of Recent Data. CME

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### Abstracts

1. Lobo RA, Kletzky OA, Kapteini EM and Goebelsmann U: Effects of alterations of plasma prolactin (PRL) levels upon circulating dehydroepiandrosterone sulfate (DHEA-S). Presented at the 61st Annual Meeting of The Endocrine Society, June 13-15, 1979, Anaheim, California.
2. Lobo RA, Paul W and Goebelsmann U: Clinical correlation between plasma dehydroepiandrosterone sulfate (DHEA-S) and urinary 17-ketosteroids (17KS) in gynecologic endocrinopathy. Presented at the American College of Obstetricians and Gynecologists, District VIII, Annual Meeting, September 16-20, 1979, Seattle, Washington.
3. Lobo RA, Paul W and Goebelsmann U: The role of DHEA-S in the evaluation of hirsute women. Presented at the 27th Annual Meeting of the Pacific Coast Fertility Society, October 17-21, 1979, Rancho Mirage, California.
4. Lobo RA and Goebelsmann U: Response of androgens and 17-hydroxyprogesterone (17OHP) to ACTH in normal and hirsute women, patients with postpubertal manifestation of congenital adrenal hyperplasia (CAH) and their family members. Presented at the 27th Annual Meeting of the Society for Gynecologic Investigation, March 19-22, 1980, Denver, Colorado.
5. Lobo RA and Goebelsmann U: Evidence for reduced 3  $\beta$ -ol- hydroxysteroid dehydrogenase (3 $\beta$ -ol-HD) activity in some hirsute women. Presented at the 27th Annual Meeting of the Society for Gynecologic Investigation, March 19-22, 1980, Denver, Colorado.
6. Mashchak CA, Lobo RA, Brenner PF and Mishell DR Jr: Comparison of pharmacodynamic properties of various estrogen formulations. Presented at the 27th Annual Meeting of the Society for Gynecologic Investigation, March 19-22, 1980, Denver, Colorado.
7. Lobo RA, March CM, Goebelsmann U and Mishell DR Jr: Subdermal estradiol ( $E_2$ ) pellets: Effects on serum  $E_2$ , estrone ( $E_1$ ), LH, FSH, binding protein, lipids and postmenopausal symptoms. Presented at the 27th Annual Meeting of the Society for Gynecologic Investigation, March 19-22, 1980, Denver, Colorado.
8. Lobo RA, March CM and Mishell DR Jr: Subdermal 17 $\beta$ -estradiol ( $E_2$ ) pellet replacement therapy in premenopausal normal and obese women. Presented at the 62nd Annual Meeting of The Endocrine Society, June 18-20, 1980, Washington, D.C.
9. Lobo RA and Goebelsmann U: Incomplete 21-hydroxylase (21OH-ase) and 3-beta-ol-hydroxysteroid dehydrogenase (3 $\beta$ -ol-HD) deficiencies in hirsute women. Presented at the 62<sup>nd</sup> Annual Meeting of The Endocrine Society, June 18-20, 1980, Washington, D.C.

10. Lobo RA, Gysler M, March CM, Goebelsmann U and Mishell DR Jr. Clinical and laboratory predictors of clomiphene response. Presented at the 28<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, October 15-19, 1980, Scottsdale, Arizona.
11. Lobo RA, Granger L, Goebelsmann U and Mishell DR Jr: Elevations in unbound serum estradiol as a possible mechanism for inappropriate gonadotropin secretion in women with PCO. Presented at the 28<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, October 15-19, 1980, Scottsdale, Arizona.
12. Lobo, RA, Paul W, Kletzky OA and March CM: Ovulatory and anovulatory hormonal profiles in women treated with high-dose clomiphene citrate (Clomid) with and without the addition of dexamethasone. Presented at the 37<sup>th</sup> Annual Meeting of The American Fertility Society, March 14-18, 1981, Atlanta, Georgia.
13. Lobo RA and Goebelsmann U: Effect of androgen excess on inappropriate gonadotropin secretion (IGS) as found in the polycystic ovary syndrome. Presented at the 28<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1981, St. Louis, Missouri.
14. Readhead CW, Lobo RA, Goebelsmann U, Kletzky O and Mishell DR Jr:  $3\beta$ -ol-hydroxysteroid dehydrogenase-isomerase enzymatic activity. Presented at the 28<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1981, St. Louis, Missouri.
15. Lobo RA, Goebelsmann U, Brenner PF and Mishell DR Jr: Effect of estrogens on adrenal androgens in oophorectomized women. Presented at the 63<sup>rd</sup> Annual Meeting of The Endocrine Society, June 17-19, 1981, Cincinnati, Ohio.
16. Readhead C, Lobo RA, Shultz AW and Kletzky OA: LH-stimulated  $3\beta$ -hydroxysteroid dehydrogenase-isomerase ( $3\beta$ -HSD) activity. Presented at the 63<sup>rd</sup> Annual Meeting of The Endocrine Society, June 17-19, 1981, Cincinnati, Ohio.
17. Granger LR, Lobo RA and Mishell DR Jr: An extended regimen of clomiphene citrate in women unresponsive to standard therapy. Presented at the 29<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, October 14-18, 1981, Rancho Mirage, California.
18. Lobo RA, Granger LR, Paul WL, Goebelsmann U and Mishell DR Jr: The relationship between psychological stress, neuro-transmitters and androgen secretion in women with PCO. Presented at the 29<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, October 14-18, 1981, Rancho Mirage, California.
19. Lahteenmaki P, Lobo R, Marrs RP, Gibbons WE, Nakamura RM and diZerega GS: folliculogenesis in response to clomiphene therapy: Allochronic follicular maturation.



Presented at the 29<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, October 14-18, 1981, Rancho Mirage, California.

20. Horton R, Lobo R and Hawks D: Plasma androstenediol glucuronide ( $3\alpha$ -diol G), a marker of peripheral androgen action in hirsutism. Presented at the Annual Meeting of the American Federation for Clinical Research, Western Society for Clinical Research, February 16-19, 1982, Carmel, California.
21. Horton R, Lobo R and Hawks D: Androstenediol glucuronide ( $3\alpha$ -diol G) in plasma: A measure of peripheral androgen action. Presented at the 7<sup>th</sup> Annual Meeting of The American Society of Andrology, February 23-26, 1982, Hilton Head Island, Southern California.
22. Lobo RA, Kletzky OA and diZerega GS: Elevated serum bioactive luteinizing hormone (LH) concentrations in women with polycystic ovary syndrome (PCO). Presented at the 38<sup>th</sup> Annual Meeting of The American Fertility Society, March 20-24, 1982, Las Vegas, Nevada.
23. Lobo RA and Kletzky OA: Elevated androgen levels and decreased SHBG in hyperprolactinemia. Presented at the 29<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 24-27, 1982, Dallas, Texas.
24. Gibbons WE, Lobo RA, Roy S and Mishell DR Jr: Estrogen receptor levels in the endometria of post-menopausal women on estrogen and progestin replacement. Presented at the 29<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 24-27, 1982, Dallas, Texas.
25. Lobo RA, Hung TT, diZerega GS, Kletzky OA and Goebelsmann U: Control of adrenal androgen secretion in women with PCO. Presented at the 29<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 24-27, 1982, Dallas, Texas.
26. Lobo RA, Goebelsmann U and Horton R:  $5\alpha$ -androstane- $3\alpha$ ,  $17\beta$ -diol-3-glucuronide ( $3\alpha$ AG), an index of increased peripheral androgen action in hirsutism. Presented at the 29<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 24-27, 1982, Dallas, Texas.
27. Lobo RA, Hung TT, Roy S and Goebelsmann U: Estrogen therapy raises serum dehydroepiandrosterone sulfate (DHEA-S) in oophorectomized (OO) women through mechanisms independent of ACTH or  $\beta$ -EP). Presented at the 29<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 24-27, Dallas, Texas.
28. Petrucha RA, Hung TT, Lobo RA and Goebelsmann U: Amniotic fluid (AF)  $\beta$ -endorphin  $\beta$ -lipotropin ( $\beta$ -EP) and  $\beta$ -LPH) concentrations during the second and third trimester.

Presented at the 29<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 24-27, 1982, Dallas, Texas.

29. Goebelsmann U, Shaaban MM, Hung TT, Hoffman DI and Lobo RA: Beta-endorphin ( $\beta$ -EP) and  $\beta$ -lipotropin ( $\beta$ -LPH) in human. Presented at the 29<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 24-27, 19982, Dallas, Texas.
30. Horton R, Lobo R and Hawks D. Androstenediol glucuronide in plasma, a marker of androgen action in men and women. Presented at the 74<sup>th</sup> Annual Meeting of the American Federation for Clinical Research, American Society for Clinical Investigation, May 8-10, 1982, Washington, D.C.
31. Lahteenmaki P, Lobo R, Marrs R, Gibbons W, Nakamura R and diZerega G: Characterization of porcine granulosa cells by isopycnic gradient centrifugation. Presented at the 64<sup>th</sup> Annual Meeting of The Endocrine Society, June 16-18, 1982, San Francisco, California.
32. Lobo RA, Goebelsmann U and Horton R: Hirsutism in polycystic ovary syndrome (PCO). Presented at the 30<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, October 13-17, 1982, Scottsdale, Arizona.
33. Montoro M, Kletzky OA, Lobo R and Nicoloff JT: Altered pituitary function in women and men with pituitary hypothyroidism. Presented at the 30<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, October 13-17, 1982, Scottsdale, Arizona.
34. Moghissi E, Lobo R, Hawks D and Horton R: Evidence for peripheral factors in the hirsutism of the polycystic ovary syndrome. Presented at the Annual Meeting of the American Federation for Clinical Research, Western Society for Clinical Research, February 9-11, 1983, Carmel, California.
35. Fallis R, Fisher M and Lobo R: A double-blind trial of naloxone in acute stroke. Presented at the Eight International Joint Conference on Stroke and Cerebral Circulation, February 10-12, 1983, San Diego, California.
36. Lobo R and Shoupe D; Evidence for decreased dopaminergic control of LH secretion in polycystic ovary syndrome (PCO): Presented at the 30<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1983, Washington, D. C.
37. Shoupe D, Campeau J and Lobo RA: Differences in bioactive (bio) LH and immunoreactive (I) LH secretion in women. Presented at the 30<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1983, Washington, D.C.
38. Marrs RP, Lobo R, Campeau JD, Brown J and diZerega GS: Correlation of human follicular fluid inhibin activity with spontaneous and induced follicular development. Presented at the 30<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March

17-20, 1983, Washington, D.C.

39. Vargyas J and Lobo R: The role of non-SHBG bound estradiol (E2), total E2, progesterone (P) and the E2/P ratio in the premenstrual syndrome (PMS). Presented at the 30<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1983, Washington, D.C.
40. Gibbons WE, Lobo RA, Moyer DL, Roy S and Mishell DR Jr; A comparison of biochemical and morphological events mediated by estrogen  $\pm$  progestin in the endometrium of postmenopausal women. Presented at the 30<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1983, Washington, D.C.
41. Shoupe D, Kumar D and Lobo R: Insulin resistance in polycystic ovary syndrome (PCO). Presented at the 30<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1983, Washington, D.C.
42. Lobo RA, Goebelsmann U and Horton R: Evidence for peripheral factors in the development of hirsutism in polycystic ovary syndrome. Presented at the 39<sup>th</sup> Annual Meeting of The American Fertility Society, April 16-20, 1983, San Francisco, California.
43. Shoupe D and Lobo RA: Insulin resistance in polycystic ovary syndrome (PCO). Presented at the 39<sup>th</sup> Annual Meeting of The American Fertility Society, April 16-20, 1983, San Francisco, California.
44. Hoffman DI and Lobo RA: The prevalence and significance of elevated DHEA-S levels in anovulatory women. Presented at the 39<sup>th</sup> Annual Meeting of The American Fertility Society, April 16-20, 1983, San Francisco, California.
45. Shoupe D and Lobo RA: Decreased dopaminergic control of LH secretion in polycystic ovary syndrome (PCO) yet differences in the control of immunological (I) LH and bioactive (bio) LH. Presented at the 65<sup>th</sup> Annual Meeting of The Endocrine Society, June 8-10, 1983, San Antonio, TX.
46. Marrs RP, Vargyas JM and Lobo R: Comparison of the intrafollicular hormone milieu with fertilization of human oocytes in vitro. Presented at the 65<sup>th</sup> Annual Meeting of The Endocrine Society, June 8-10, 1983, San Antonio, Texas.

47. Lobo RA, Vargyas JM and Marrs RP: Androgen levels in follicular fluid (FF) and its relationship to the maturity of the oocyte and its ability to be fertilized in vitro. Presented at the 31<sup>st</sup> Annual Meeting of the Pacific Coast Fertility Society, October 12-16, 1983, Rancho Mirage, California.
48. Ablan F, Moghissi M, Hoopes M, Lobo RA and Horton R: Origin of androstanediol glucuronide in plasma of men and women with polycystic ovary syndrome. Presented at the annual Meeting of the American Federation for Clinical Research, Western Society for Clinical Research, February 8-10, 1984, Carmel, California.
49. Serafini P and Lobo R; Androgenicity in women; Tissue 5 $\alpha$ -reductase activity (5 $\alpha$ -RA) and serum androgen levels. Presented at the 31<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1984, San Francisco, California.
50. Serafini P and Lobo R: Hirsutism in postmenopausal women (PoW): Androgen/estrogen ratios and 5 $\alpha$ -reductase activity (5 $\alpha$ -RA). Presented at the 31<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1984, San Francisco, California.
51. Shoupe D, Chang SP, Kletzky OA and Lobo R: Differences in the ratio of bioactive to immunoreactive serum LH during vasomotor flushes and hormonal therapy in postmenopausal women. Presented at the 31<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1984, San Francisco, California.
52. Shoupe D, Montz FJ and Lobo R: LH and PRL-evoked naloxone (Nal) responses and plasma  $\beta$ -EP in oophorectomized women (Ow) before and after estrogen (E) and progestin (P) treatment. Presented at the 31<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1984, San Francisco, California.
53. Serafini P, Goebelsmann UT and Lobo RA: Increased 5 $\alpha$ -reductase activity in hirsutism. Presented at the 40<sup>th</sup> Annual Meeting of The American Fertility Society, April 2-7, 1984, New Orleans, Louisiana.
54. Lobo R, Shoupe D, Serafini P, Brinton D and Horton R: Serum androgens and the clinical response to spironolactone therapy. Presented at the 40<sup>th</sup> Annual Meeting of The American Fertility Society, April 2-7, 1984, New Orleans, Louisiana.
55. Shoupe D and Lobo RA: PRL responses after GnRH in PCO. Presented at the 40<sup>th</sup> Annual Meeting of The American Fertility Society, April 2-7, 1984, New Orleans, Louisiana.
56. Serafini P, Ablan F, Horton R and Lobo R: The effects of spironolactone and progesterone on in vitro 5 $\alpha$ -reductase activity in hirsute women. Presented at the International Symposium on Regulation of Androgen Action, June 29-July 1, 1984, Montreal, Quebec, Canada.

57. Serafini P, Ablan F and Lobo R: Increased in vitro production of DHT-glucuronide (G) and  $3\alpha$ - androstenediol ( $3\alpha$ -diol) G from the skin of hirsute women. Presented at the 7<sup>th</sup> International Congress of Endocrinology, July 1-7, 1984. Quebec City, Quebec, Canada.
58. Shoupe D, Barnes RB, Montz FJ, Brazal SD and Lobo R: Bioactive (bio) LH and the bio: immunoreactive (i) LH ratio after naloxone (nal) as a probe for endogenous central opioid activity (COA) in women. Presented at the 7<sup>th</sup> International Congress of Endocrinology, July 1-7, 1984, Quebec City, Quebec, Canada.
59. Barnes R, Shoupe D and Lobo R: Endogenous opioid activity in polycystic ovary syndrome. Presented at the 7<sup>th</sup> International Congress of Endocrinology, July 1-7, 1984, Quebec City, Quebec, Canada.
60. Hoffman D, Lobo R, Platt L and diZerega G: Differential follicular response in anovulatory patients to purified urinary FSH versus purified urinary FSH and LH. Presented at the Vth Reinier de Graaf Symposium: Gamete Quality and Fertility Regulation, August 23-25, 1984, Nijmegen, The Netherlands.
61. Serafini P and Lobo R: The effects of spironolactone on adrenal steroidogenesis in hirsute women. Presented at the 32<sup>nd</sup> Annual Meeting of the Pacific Coast Fertility Society, September 19-23, 1984, Rancho Mirage, California.
62. Barnes R, Shoupe D, Chiang J and Lobo R: Central opioid activity in polycystic ovary syndrome. Presented at the 32<sup>nd</sup> Annual Meeting of the Pacific Coast Fertility Society, September 19-23, 1984, Rancho Mirage, California.
63. Vargyas J, Lobo R and Mishell D: Brain opioid activity in the premenstrual cycle. Presented at the 32<sup>nd</sup> Annual Meeting of the Pacific Coast Fertility Society, September 19-23, 1984.
64. Hoffman DI, Lobo R, Moyer D, Roy S and Platt L: Evaluation of early follicular phase administration of a potent gonadotropin-releasing hormone agonist (Wy-40, 972, Wyeth). Presented at the 32<sup>nd</sup> Annual Meeting of the Pacific Coast Fertility Society, September 19-23, 1984, Rancho Mirage, California.
65. Steingold KA, Lobo R, Andrews L, Lu JKH, Judd HL and Chang RJ: The effect of bromocriptine on gonadotropin secretion in polycystic ovary disease. Presented at the 32<sup>nd</sup> annual Meeting of the Pacific Coast Fertility Society, September 19-23, 1984, Rancho Mirage, California.
66. Lobo RA and Serafini PC: Peripheral androgen metabolism (PAM) in postmenopausal (PM) women and the complaint of hirsutism. Presented at The Fourth International Congress on the Menopause, October 28-November 2, 1984, Orlando, Florida.

67. Barnes R, Roy S and Lobo R: Plasma lipid and serum androgen levels in postmenopausal (PM) women treated with depo-medroxyprogesterone acetate (DMPA). Presented at The Fourth International Congress on the Menopause, October 28-november 2, 1984, Orlando, Florida.
68. Serafini P, Paulson F, Elkind-Hirsch K, Hernandez M and Lobo R: Acute modulation of the hypothalamic pituitary axis (HPA) by testosterone (T) in normal women. Presented at the 32<sup>nd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1985, phoenix, Arizona.
69. Baranes R, Cha K and Lobo R: Altered dopaminergic control of PRL in polycystic ovary syndrome (PCO). Presented at the 32<sup>nd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1985, Phoenix, Arizona.
70. Barnes R, Lee D and Lobo R: Dopamine but not norepinephrine influences the bioactivity of LH in normal women. Presented at the 32<sup>nd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1985, Phoenix, Arizona.
71. Paulson R, Serafini P, Catalino J and Lobo R: Serum and urinary 3  $\alpha$ -androstenediol glucuronide 3 $\alpha$ -diol G) and their correlations with genital skin 5 $\alpha$ -reductase activity (5 $\alpha$ RA) and 3 $\alpha$ -diol G formation. Presented at the 32<sup>nd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1985, Phoenix, Arizona.
72. Baranes RB, Chiang JH, Cha KY, Shoupe D and Lobo R: Responses of bio and iLH and FSH to 2 doses of a nasal GnRH agonist. Presented at the 33<sup>rd</sup> Annual Meeting of the Pacific Coast Fertility Society, April 24-28, 1985, Las Vegas, Nevada.
73. Paulson RJ, Bernstein GS and Lobo RA: Idiopathic oligospermia and peripheral androgen metabolism. Presented at the 33<sup>rd</sup> Annual Meeting of the Pacific Coast Fertility Society, April 24-28, 1985, Las Vegas, Nevada.
74. Serafini PC and Lobo RA: Prolactin (PRL) modulates peripheral androgen metabolism (PAM). Presented at the 33<sup>rd</sup> Annual Meeting of the Pacific Coast Fertility Society, April 24-28, 1985, Las Vegas, Nevada.
75. Serafini P, Paulson R, Francis M and Lobo R: Testosterone elicits divergent PRL and LH responses after GnRH in normal women. Presented at the 67<sup>th</sup> Annual Meeting of The Endocrine Society, June 19-21, 1985, Baltimore, Maryland.
76. Barnes R, Artal R and Lobo R: Altered catecholamine metabolism in polycystic ovary syndrome (PCO). Presented at the 67<sup>th</sup> Annual Meeting of The Endocrine Society, June 19-21, 1985, Baltimore, Maryland.
77. Greep N, Hoopes M, Lobo R and Horton R: Evidence for a role of androstenedione as precursor of plasma DHT and androstenediol glucuronide in normal hirsute women.

Presented at the 67<sup>th</sup> Annual Meeting of The Endocrine Society, June 19-21, 1985, Baltimore, Maryland.

78. Lobo RA, Serafini PC and Paulson RJ: Genital skin 5 $\alpha$ -reductase activity (5 $\alpha$ RA): A marker of androgenicity in women. Presented at the 4<sup>th</sup> Annual Meeting of The American Gynecological and Obstetrical Society, September 4-7, 1985, Hot Springs, Virginia.
79. Mileikowsky G, Anderson R, Chen D, Siegel M and Lobo R: Radionuclide hysterosalpingo tomography (RHST) for the evaluation of the reproductive tract in infertility. Presented at the 41<sup>st</sup> Annual Meeting of The American Fertility Society, September 27-October 2, 1985, Chicago, Illinois.
80. Barnes R, Spencer C and Lobo R: Responses of LH, PRL and TSH to dopaminergic blockade in polycystic ovary syndrome (PCO): Lack of evidence for decreased dopaminergic activity. Presented at the 41<sup>st</sup> Annual Meeting of The American Fertility Society, September 27-October 2, 1985, Chicago, Illinois.
81. Cha K, Barnes R, Marrs R and Lobo R: Oocyte maturity in the spontaneous cycle correlates with follicular fluid (FF) progesterone (Prog) levels and LH of greater biological activity. Presented at the 41<sup>st</sup> Annual Meeting of The American Fertility Society, September 27-October 2, 1985, Chicago, Illinois.
82. Paulson R, Serafini P and Lobo R: Effect of sex steroids on 5 $\alpha$ -reductase activity (5 $\alpha$ RA) in vitro. Presented at the 41<sup>st</sup> Annual Meeting of The American Fertility Society, September 27-October 2, 1985, Chicago, Illinois.
83. Hoffman D, Lobo R, Campeau J and diZerega G: Increased prolactin (PRL) levels in gonadotropin-stimulated cycles. Presented at the 41<sup>st</sup> Annual Meeting of The American Fertility Society, September 27-October 2, 1985, Chicago, Illinois.
84. Cha K, Campeau J, Marrs R, Nakamura R and Lobo R: Follicular fluid (FF) LH bioactivity and oocyte maturity (OM) in spontaneous (S) and stimulated (STIM) cycles. Presented at the 33<sup>rd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 19-22, 1986, Toronto, Ontario, Canada.
85. Paulson RJ, Paulson YJ, Silva PD, Cha KY, Lobo RA, Yee B and Marrs RP: Hormonal dynamics of hCG-triggered ovulation: Bio-hCG and steroid response. Presented at the 33<sup>rd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 19-22, 1986, Toronto, Ontario, Canada.
86. Shoupe D, Spitz I, Osborn C, Page M, Mishell D Jr and Lobo R: Effects of progesterone (P) antagonism on gonadotropins at midcycle and during the luteal phase. Presented at the 33<sup>rd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 19-22, 1986, Toronto, Ontario, Canada.

87. Silva P, Paulson R, Serafini P, Francis M and Lobo R: Acute effects of testosterone (T) on immunoreactive luteinizing hormone (ILH) and bioreactive LH (BLH) in normal women. Program book of the 33<sup>rd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 19-22, Toronto, Ontario, Canada.
88. Paulson R, Gentzschein E, Nguyen H and Lobo R: Differences between genital skin (G) and pubic (P) skin 5 $\alpha$ -reductase activity (5 $\alpha$ RA). Program book of the 33<sup>rd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 19-22, 1986, Toronto, Ontario, Canada.
89. Silva P, Gentzschein E, Paulson R, Horton R and Lobo R: Androstenedione (A) as precursor for DHT: Evidence for dissociated blood and tissue DHT production (P). Program book of the 33<sup>rd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 19-22, 1986, Toronto, Ontario, Canada.
90. Paulson RJ, Silva PD, Paulson YJ, Cha KY, Yee B, Lobo RA and Marrs RP: The effects of different doses of intramuscular hCG on follicular fluid (FF) steroid and hCG levels and on oocyte maturity (OM). Presented at the 34<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 9-13, 1986, San Diego, California.
91. Rosen GF, Vermesh M, Gentzschein E and Lobo RA: Clinical heterogeneity in Turner's syndrome. Presented at the 34<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 9-13, 1986, San Diego, California.
92. Silva PD, Porto M, Moyer DL and Lobo RA: Expression of androgenicity in a nonsteroid secreting tumor in pregnancy. Presented at the 34<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, 9-13, 1986, San Diego, California.
93. Rosen GF and Lobo RA: Further evidence against dopamine (DA) deficiency as a cause of inappropriate gonadotropin secretion (IGS) in polycystic ovary syndrome (PCO). Presented at the 42<sup>nd</sup> Annual Meeting of The American Fertility Society/Canadian Fertility and Andrology Society, September 27-October 2, 1986, Toronto, Ontario, Canada.
94. Silva PD and Lobo RA: Androstenedione (A) is the major precursor of tissue dihydrotestosterone (DHT)-production (P) in women. Presented at the 42<sup>nd</sup> Annual Meeting of The American Fertility Society/Canadian Fertility and Andrology Society, September 27- October 2, 1986, Toronto, Ontario, Canada.
95. Rosen GF, Cha K-Y, Marrs RP and Lobo RA: Effects of pure FSH (Metrodin) and HCG on hormonal characteristics on follicular fluid (FF) and their correlation with oocyte maturity (OM). Presented at the 42<sup>nd</sup> Annual Meeting of The American Fertility Society/Canadian Fertility and Andrology Society, September 27-October 2, 1986, Toronto, Ontario, Canada.
96. Xu YK, Ng, WG, Kaufman F, Lobo R and Donnell GN: Galactose metabolism in human



- ovary. Presented at the Annual Meeting of the American Federation for Clinical Research, Western Society for Pediatric Research, February 3-6, 1987, Carmel, California.
97. Pasupuleti V, Lobo R and Horton R: Formation of androstenediol glucuronide by human sexual skin. Presented at the Annual Meeting of the American Federation for Clinical Research, Western Society for Clinical Research, February 3-6, 1987, Carmel, California.
  98. Lobo R, Gentzschlein E, Pasupuleti V and Horton R: Differential pathways of  $3\alpha$ -diol G formation in human skin. Presented at the 34<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1987, Atlanta, Georgia.
  99. Vermesh M, Silva PD and Lobo R: Opiates modulate the inhibitory effect of androgen on the hypothalamic-pituitary axis (HPA) of normal women. Presented at the 34<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1987, Atlanta, Georgia.
  100. Davidson A, Vermesh M, Vijod A, Paulson RJ and Lobo R: Presence of immunoreactive  $\beta$ -endorphin ( $\beta$ EP) in seminal plasma (SP) and its possible involvement in sperm motility. Presented at the 34<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1987, Atlanta, Georgia.
  101. Kaufman F, Xu Y, Ng W, Donnell G and Lobo R: Characterization of ovarian failure in galactosemia (G) and galactose (gal) metabolism in the ovary. Presented at the 34<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1987, Atlanta, Georgia.
  102. Lobo R, Nguyen H, Eggena P and Brenner P: Biological effects of equilin sulfate (EqS): Differences in hepatic and bone resorbing effects. Presented at the 34<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1987, Atlanta, Georgia.
  103. Paulson RJ, Do Y, Hsueh W, Eggena P and Lobo R: Prorenin (PR), renin activity (RA) and renin substrate (RS) in follicular fluid (FF): Correlation with oocyte maturity (OM) and FF steroids. Presented at the 34<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1987, Atlanta, Georgia.
  104. Shoupe D, Roy S and Lobo RA: Psychological function (Psy) and peripheral and central opioid activity (COA) in postmenopausal women (PM): Estrogen and progestin effects. Presented at the 34<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1987, Atlanta, Georgia.
  105. Vermesh M, Silva PD, Rosen GF and Lobo R: Induction of partial 21-hydroxylase deficiency by androgen in normal women. Program book of the 34<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1987, Atlanta, Georgia.

106. Davidson A, Vermesh M, Toker R, Braxton P, Lobo R and Paulson R: Mouse embryo culture as quality control for human IVF: The once cell (1C) vs. two cell (2C) model. Presented at the Vth World Congress - In Vitro Fertilization and Embryo Transfer, April 5-10, 1987, Norfolk, Virginia.
107. Lobo RA, Cristo M and Crary W: Effects of estrogen on psychological function in asymptomatic postmenopausal women. Presented at the Fifth International Congress on the Menopause, April 6-10, 1987, Sorrento, Italy.
108. Nguyen HN, Eggena P and Lobo RA: Biological effects of equilin sulfate; Differences in hepatic and bone resorbing effects. Presented at the Fifth International Congress on the Menopause, April 6-10, 1987, Sorrento, Italy.
109. Morton J, Fraser D, Whitehead MI and Lobo R: Is failure of progesterone action upon the endometrium due to poor end-organ response or to poor absorption/rapid metabolism of the progestogen? Presented at the Fifth International Congress on the Menopause, April 6-10, 1987, Sorrento, Italy.
110. Anderson RE, Ben-Rafael Z, Meloni L, Flickinger M, Barnes RB, Rosen GF and Lobo RA: Secretory dynamics of bioactive and immunoreactive PRL in PCO. Presented at the 35<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, May 6-10, 1987, Palm Springs, California.
111. Davidson A, Vermesh M, Lobo RA and Paulson RJ: The temporal effects of changes in IVF culture media on the one-cell (1C) mouse embryo system. Presented at the 35<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, May 6-10, 1987, Palm Springs, California.
112. Davidson A, Vermesh M, Vijod AG, Paulson RJ and Lobo RA: The presence of calcitonin in seminal plasma. Presented at the 35<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, May 6-10, 1987, Palm Springs, California.
113. Silva PD, Paulson RJ, Anderson RE, Werlin LB, Stein AL and Lobo RA: Ectopic pregnancy in contralateral tubal remnants after unilateral tubal anastomosis: Preventable and unpreventable causes. Presented at the 35<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, May 6-10, 1987, Palm Springs, California.
114. Stein A, Manoogian C, Vijod A and Lobo R: Adrenal androgen excess resulting in virilization and PCO-like features. Presented at the 35<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, May 6-10, 1987, Palm Springs, California.
115. Vermesh M, Silva PD, Rosen GF and Lobo RA: Adrenal effects of short-term administration of testosterone in normal women. Presented at the 35<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, May 6-10, 1987, Palm Springs, California.

116. Stanczyk FZ, Kaufman FR, Gentzschein E and Lobo RA: Androstenedione (A) is an important precursor of dihydro-testosterone (DHT) in the skin of women and is metabolized via  $5\alpha$ -androstenedione ( $5\alpha$ -A). Presented at the 69<sup>th</sup> Annual Meeting of The Endocrine Society, June 10-12, 1987, Indianapolis, Indiana.
117. Shoupe D, Mishell DR Jr, Tonetta SA, Spitz IM, Madkour H and Lobo RA: Suppression of ovulation by follicular phase administration of the antiprogestin RU 486 and evidence for suppression of ovarian steroidogenesis. Presented at the 69<sup>th</sup> Annual Meeting of The Endocrine Society, June 10-12, 1987, Indianapolis, Indiana.
118. Pasupuleti V, Lobo R and Horton R: Conversion of dihydrotestosterone to androstenediol glucuronide by skin. Presented at the 69<sup>th</sup> Annual Meeting of The Endocrine Society, June 10-12, 1987, Indianapolis, Indiana.
119. Davidson A, Vermesh M, Lobo RA and Paulson RJ: The temporal effects of changes in IVF culture media on the one-cell (1C) mouse embryo system. Presented at the 43<sup>rd</sup> Annual Meeting of The American Fertility Society, September 28-30, 1987, Reno, Nevada.
120. Stein AL and Lobo RA: Factors determining clitoral hypertrophy (CH) in hyperandrogenism. Presented at the 43<sup>rd</sup> Annual Meeting of The American Fertility Society, September 28-30, 1987, Reno, Nevada.
121. Anderson R, Cragun J, Chang RJ, Bhasin S, Stanczyk F, Vijod M and Lobo RA: Pharmacodynamics of human urinary FSH (hFSH) and human menopausal gonadotropin hMG) in PCO and normal women. Presented at the 35<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1988, Baltimore, Maryland.
122. Shoupe D, Mishell DR Jr and Lobo R: Evidence that oxytocin increases cortisol secretion and decreases LH pulsatility in normal women. Presented at the 35<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1988, Baltimore, Maryland.
123. Matteri RK, Stanczyk FZ, Kaufman FR, Vijod AG, Anderson RE and Lobo RA: Measurement and comparison of circulating C19 sulfates and glucuronides in normal and hirsute women and men. Presented at the 35<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1988, Baltimore, Maryland.
124. Paulson RJ, Do Y, Hsueh W and Lobo R: Prorenin (PR) and renin activity (RA) in ovarian venous (OV) and peripheral venous (PV) blood: Gradients and correlations with ovarian steroids. Presented at the 35<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1988, Baltimore, Maryland.
125. Kaufman FR, Matteri RK, Stanczyk FZ, Gentzschein E, Delgado C and Lobo RA: Characterization of dehydroepiandrosterone (DHEA) and DHEA-sulfate (S) metabolism

in

- human genital skin. Presented at the 35<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1988, Baltimore, Maryland.
126. Stanczyk FZ, Shoupe D, Nunez V and Lobo RA: A randomized comparison of non-oral estradiol (E2) delivery in post-menopausal women (PM). Presented at the 35<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1988, Baltimore, Maryland.
  127. Matteri RK, Stanczyk FZ, Kaufman FR, Chenette PE, Anderson RE, Gentzschein E and Lobo RA: Androgen sulfates as markers of peripheral androgen action in hirsutism. Presented at the 36<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 13-17, 1988, Palm Springs, California.
  128. Anderson RE, Stein AL, Paulson RJ and Lobo RA: Effects of norethindrone (NET) used to program oocyte retrieval for in vitro fertilization. Presented at the 36<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 13-17, 1988, Palm Springs, California.
  129. Shoupe D, Mishell DR, Lobo RA, Lacarra M, Horenstein J, d'Ablaining G, Moyer D: Correlation of endometrial maturation with 4 methods of estimating day of ovulation. Presented at the 36<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 13-17, 1988, Palm Springs, California.
  130. Graczykowski JW, Vermesh M, Siegel MS and Lobo RA: The effect of beta-endorphin ( $\beta$ -EP) and calcitonin (CT) on sperm movement characteristics in vitro. Presented at the 36<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 13-17, 1988, Palm Springs, California.
  131. Matteri RK, Stanczyk FZ, Kaufman FR, Delgado C, Gentzschein E and Lobo RA: Production of C19 sulfates and glucuronides in human genital skin. Presented at the 70<sup>th</sup> Annual Meeting of The Endocrine Society, June 8-11, 1988, New Orleans, Louisiana.
  132. Carmina E, Malizia G, Janni A and Lobo RA: Comparison of adrenal responses with ACTH and ovine (O) CRF in normal and hyperandrogenic women. Presented at the 70<sup>th</sup> Annual Meeting of The Endocrine Society, June 8-11, 1988, New Orleans, Louisiana.
  133. Matteri R, Hatch I, Delgado C, Paulson R, Stanczyk F and Lobo R: Influence of the ovary on androgens of peripheral origin. Presented at the 44<sup>th</sup> Annual Meeting of The American Fertility Society, October 8-13, 1988, Atlanta, Georgia.
  134. Anderson RE, Paulson RJ, Sauer MV and Lobo RA: Evidence supporting the routine use of a GnRH agonist (GnRH-a) during ovarian stimulation for in vitro fertilization (IVF). Presented at the 4<sup>th</sup> Annual Meeting of The American Fertility Society, October 8-13, 1988, Atlanta, Georgia.
  135. Vermesh M, Silva PD, Rosen GF, Stein AL, Fossum GT, Anderson RE, Sauer MV,

- Vargyas JM, Lobo RA and Mishell DR Jr: Management of unruptured ectopic pregnancy (UEP) by linear salpingostomy (LS). An extended, prospective clinical trial of laparoscopy (LSC) versus laparotomy. Presented at the 44<sup>th</sup> Annual Meeting of the American Fertility Society, October 8-13, 1988, Atlanta, Georgia.
136. Levin JH, Anderson RE, Stanczyk FZ and Lobo RA: Characteristics of progestin (P) inhibition of gonadotropin secretion in normal women. Presented at the 36<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1989, San Diego, California.
  137. Matteri RK, Stanczyk FZ, Lee DG, Delgado C, Gentzschein E and Lobo RA: C-19 conjugates reflect both ovarian and peripheral androgen metabolism. Presented at the 36<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1989, San Diego, California.
  138. Matteri RK, Stanczyk FZ, Gentzschein E, Vijod AG and Lobo RA:  $\Delta^5$  androstenediol and its conjugates in pre and post-menopausal women and men. Presented at the 36<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1989, San Diego, California.
  139. Stanczyk FZ, Nadler J, Vijod AG, Krikorian L, Rosen GF, Steinleitner A and Lobo RA: Influence of estrogen and the effect of smoking on prostacyclin (PGI<sub>2</sub>) and thromboxane A<sub>2</sub> (TXA<sub>2</sub>) balance in postmenopausal women. Presented at the 36<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1989, San Diego, California.
  140. Steinleitner A, Stanczyk FZ, Levin JH, Vijod MA, Nakamura RM and Lobo RA: Decreased production of 6-keto-prostaglandin (F<sub>1 $\alpha$</sub> ) (6KPGF<sub>1 $\alpha$</sub> ) by postmenopausal uterine arteries. Presented at the 36<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1989, San Diego, California.
  141. Steinleitner A, Stanczyk FZ, Paulson RJ and Lobo RA: Characterization of proopiomelanocortin (POMC) peptides in porcine and human follicular fluid. Presented at the 36<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1989, San Diego, California.
  142. Paulson RJ, Hernandez MF, Do YS, Hsueh WA and Lobo RA: Angiotensin II (AII) modulation of steroidogenesis by luteinized granulosa cells in vitro. Presented at the 36<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1989, San Diego, California.
  143. Carmina E, Levin JH, Malizia G and Lobo RA: Decreased responses of ACTH to ovine corticotropin-releasing factor (oCRF) and increased adrenal insensitivity in hyperandrogenic women. Presented at the 37<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 12-16, 1989, Palm Springs, California.
  144. Paulson RJ, Francis-Hernandez M, Macaso TM, Lobo RA and Sauer MV: Embryo

implantation following human in vitro fertilization (IVF): Relative contributions of embryo quality (EQ) and endometrial receptivity (ER). Presented at the 37<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 12-16, 1989, Palm Springs, California.

145. Sauer MV, Macaso TM, Francis-Hernandez M, Lobo RA and Paulson RJ: Establishment of a non-anonymous donor oocyte program: Preliminary experience at the University of Southern California. Presented at the 37<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 12-16, 1989, Palm Springs, California.
146. Carmina E, Levin JH and Lobo RA: Clinical similarities between late onset congenital adrenal hyperplasia and polycystic ovary syndrome. Presented at the 71<sup>st</sup> Annual Meeting of The Endocrine Society, June 21-24, 1989, Seattle, Washington.
147. Matteri RK, Kaufman FR, Stanczyk FZ, Gentzschein E, Vijod AG and Lobo RA: Androgens of peripheral origin increase during adrenarche in boys. Presented at the 71<sup>st</sup> Annual Meeting of The Endocrine Society, June 21-24, 1989, Seattle, Washington.
148. Matteri RK, Levin JH, Stanczyk FZ, Paulson RJ and Lobo RA: Androgens are elevated with gonadotropin therapy despite GnRH-agonist suppression. Presented at the 45<sup>th</sup> Annual Meeting of The American Fertility Society, November 11-16, 1989, San Francisco, California.
149. Carmina E, Stanczyk FZ, Matteri RK and Lobo RA: Androsterone glucuronide signifies the presence and severity of acne (A) among hyperandrogenic hirsute women (HHW). Presented at the 37<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.
150. Lee DG, Pike MC, Stanczyk FZ and Lobo RA: A reevaluation of the effects of smoking on estrogen status. Presented at the 37<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.
151. Presser SC, Stanczyk FZ and Lobo RA: The simultaneous measurements of prostacyclin and thromboxane metabolites during the menstrual cycle and in postmenopausal women. Presented at the 37<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.
152. Levin, JH, Tonetta SA, Hickey MJ and Lobo RA; Growth factors modulate prolactin (PRL) production by isolated, dispersed human endometrial stromal cells in culture. Presented at the 37<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.
153. Levin JH, Tonetta SA, Stanczyk FZ and Lobo RA: Differential regulation of prolactin (PRL) and prostacyclin production by human endometrial stromal cells in culture.

Presented at the 37<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.

154. Levin JH, Hickey MJ and Lobo RA: Mechanisms of clomiphene citrate (CC) resistance in polycystic ovary syndrome (PCO). Presented at the 37<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.
155. Stanczyk FZ, Moltz L, Schwartz U and Lobo RA: Dexamethasone (DEX) suppressibility and adrenal and ovarian venous effluents of 5 $\alpha$ -reduced C19 conjugates in women. Presented at the 37<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.
156. Steinleitner A, Stanczyk FZ and Lobo RA: Production of POMC peptides under gonadotropin stimulation and modulation of ovarian steroidogenesis by POMC peptides in cultured porcine granulosa cells (pGC). Presented at the 37<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.
157. Sauer MV, Paulson RJ and Lobo RA: Oocyte donation: Extending reproductive potential to women over forty. Presented at the 37<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.
158. Paulson RJ, Sauer MV and Lobo RA: Factors affecting embryo implantation (EI) following human in vitro fertilization (IVF). Presented at the 37<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.
159. Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: In vitro fertilization (IVF) in unstimulated cycles. Presented at the 37<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.
160. Price T, Dupuis R, Pollack G, Mattern W, Stanczyk F, Lobo R, Dotters D and Droegemueller W: Single dose pharmacokinetics of a 35  $\mu$ g ethinyl estradiol, 1 mg norethindrone combination oral contraceptive in women with chronic renal failure on continuous ambulatory peritoneal dialysis. Presented at the 37<sup>th</sup> Annual Meeting of the Society for gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.
161. Kovacs BW, Kornafel K, Shahbahrani B, Curtain J and Lobo R: Molecular alterations in endometrial hyperplasias and cancers. Presented at the 37<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.
162. Sauer MV, Paulson RJ, Macaso TM, Francis MM and Lobo RA: Nonanonymous oocyte donation: A successful treatment for infertility in women with ovarian failure. Presented at the 38<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 25-29, 1990, Scottsdale, Arizona.
163. Frederick JL, Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: In vitro fertilization (IVF) in unstimulated cycles: Analysis of follicular fluid (FF) steroids.

Presented at the 38<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 25-29, 1990, Scottsdale, Arizona.

164. Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: Use of test-yolk buffer (TYB) to enhance fertilization during human in vitro fertilization (IVF) in cases of suspected male infertility. Presented at the 38<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 25-29, 1990, Scottsdale, Arizona.
165. Levin JH, Tonetta SA and Lobo RA: Human chorionic gonadotropin (hCG) enhances progesterin stimulation of prolactin (PRL) production by human endometrial stromal cells in culture: Evidence for trophoblast-endometrial paracrine interaction. Presented at the 38<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 25-29, 1990, Scottsdale, Arizona.
166. Levin JH, Tonetta SA and Lobo RA: Leuprolide acetate (LA) does not alter progesterin stimulation of prolactin (PRL) production by human endometrial stromal cells in culture. Presented at the 38<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 25-29, 1990, Scottsdale, Arizona.
167. Carmina E and Lobo RA: Serum levels of 5 androgen metabolites in hirsutism. Presented at the XXIII Congresso Della Societa Italiana di Endocrinologia, May 27-29, 1990, Porto Conte-Alghero, Italy.
168. Carmina E and Lobo RA: Effect of long term dexamethasone (DEX) or spironolactone (S) administration on clinical presentation and peripheral androgen metabolites in hirsutism. Presented at the 2<sup>nd</sup> European Congress of Endocrinology, July 1-6, 1990, Ljubljana, Yugoslavia.
169. Stanczyk FZ, Matteri RK and Lobo RA: An assessment of serum C<sub>19</sub> sulfates and glucuronides as markers of peripheral androgen metabolism in women. Presented at the VIII International Congress on Hormonal Steroids, September 16-21, 1990, The Hague, The Netherlands.
170. Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: Norethindrone (NET) blocks the initial agonistic response to leuprolide acetate (LA). Presented at the 46<sup>th</sup> Annual Meeting of The American Fertility Society, October 13-18, 1990, Washington, D.C.
171. Ditkoff EC, Cassidenti DL, Paulson RJ, Sauer MV, Paul WL and Lobo RA: The GnRH antagonist, Nal-Glu, acutely blocks the LH surge but allows for resumption of folliculogenesis in normal women and in women undergoing hyperstimulation. Presented at the 38<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991,



San Antonio, Texas.

172. Cassidenti DL, Sauer MV, Paulson RJ, Ditkoff EC and Lobo RA: A proposed protocol for the use of the GnRH-antagonist (Nal-Glu) in IVF cycles and its comparison to the GnRH-agonist (A). Presented at the 38<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.
173. Miles RA, Cassidenti DL, Carmina E, Gentzschein E, Stanczyk FZ and Lobo RA: Percutaneous androstenedione as an in vivo test of inherent  $5\alpha$ -reductase activity ( $5\alpha$ -RA). Presented at the 38<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.
174. Cassidenti DL, Stanczyk FZ and Lobo RA: The relationship between insulin resistance, IGF-1 levels, adrenal androgens and peripheral androgen metabolism in polycystic ovary syndrome (PCO). Presented at the 38<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.
175. Stanczyk FZ, Chang L, Carmina E and Lobo RA: Is  $11\beta$ -hydroxyandrostenedione ( $11\beta$ -OHA) a better marker of adrenal androgen excess than dehydroepiandrosterone (DS)? Presented at the 38<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.
176. Levin JH, Stanczyk FZ, Vijod MA and Lobo RA: Growth factors stimulate prostaglandin production from human endometrial stromal cells in culture. Presented at the 38<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.
177. Chang L, Stanczyk FZ, Cassidenti DL, Putz Z and Lobo RA: Is the ovary a source of  $11\beta$ -hydroxyandrostenedione among hyperandrogenic women? Presented at the 38<sup>th</sup> Annual Meeting of the Soc. for Gynecol Invest. March 20-23, 1991, San Antonio, Texas.
178. Presser SC, Stanczyk FZ, Delgado C and Lobo RA: Insulin sensitivity in postmenopausal women and the effects of estrogen. Presented at the 38<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.
179. Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: Factors affecting success of human in vitro fertilization (IVF) in unstimulated cycles. Presented at the 38<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.
180. Bergman A, Lobo R and Stanczyk FZ: Role of prostaglandins in detrusor instability. Presented at the 38<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.
181. Dodds WG, Friedman CI, Lobo R, Goldberg J and Kim MH: Low dose daily verses

- alternate day dexamethasone therapy in adrenal hyperandrogenism. Presented at the 38<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.
182. Meme D, Shoupe D and Lobo R: Use of progesterone (P) releasing intrauterine device for protection of the endometrium in menopausal hormone replacement: A pilot study. Presented at the 38<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.
  183. Cassidenti DL, Paulson RJ, Lobo RA and Sauer MV: The synergistic effects of clomiphene citrate and human menopausal gonadotropins in folliculogenesis of hyperstimulated cycles as assessed by GnRH antagonist (Nal-Glu). Presented at the 39<sup>th</sup> Annual Meeting of the Pacific coast Fertility Society, April 10-14, 1991, Indian Wells, California.
  184. Presser SC, Stanczyk FZ, Sauer MV, Delgado C and Lobo RA: Insulin induced stress responses and the effects of estrogen and progestin in postmenopausal women (PMW). Presented at the 39<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 10-14, 1991, Indian Wells, California.
  185. Carmina E, Stanczyk FZ, Chang L, Miles RA and Lobo RA: The ratio of androstenedione (A)/11 $\beta$ -hydroxyandrostenedione (11 $\beta$ -A) is an important marker of adrenal androgen excess in women. Presented at the 39<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 10-14, 1991, Indian Wells, California.
  186. Cassidenti DL, Matteri RK, Vijod AG and Lobo RA: Lack of correlation between the suppression of androgen levels and the ovulatory response in clomiphene resistant patients with polycystic ovary syndrome (PCO). Presented at the 39<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 10-14, 1991, Indian Wells, California.
  187. Paulson RJ, Sauer MV, Francis MM, Macaso M and Lobo RA: Embryo implantation after in vitro fertilization (IVF) in unstimulated cycles. Presented at the 39<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 10-14, 1991, Indian Wells, CA.
  188. Ditkoff EC, Levin JH, Paul WL, and Lobo RA: Time-related fluorimmunoassay (FIA): A better clinical indication of LH biological activity. Presented at the 47<sup>th</sup> Annual Meeting of The American Fertility Society, October 19-24, 1991, Orlando, Florida.
  189. Carmina E, Ditkoff EC, Vijod AG, Janni A and Lobo RA: Increased circulating levels of  $\beta$ -endorphin in PCO are not due to increased pituitary secretion. Presented at the 39<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.
  190. Millar LK, Goodwin TM, Stanczyk FZ, Lobo RA and Paul RH: Effect of 6 hour

infusion of the oxytocin antagonist atosiban on uterine activity and plasma PGFM.  
Presented at the 39<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation,  
March 18-21, 1992, San Antonio, Texas.

191. Ng S, Shoupe D and Lobo R: Peripheral vasodilatory effect of conjugated equine estrogens in postmenopausal women. Presented at the 39<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.
192. Lindheim SR, Legro RS, Stanczyk FZ, Vijod MA and Lobo RA: Stress responses in pre- and postmenopausal women and the effects of estrogen. Presented at the 39<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.
193. Ditkoff EC, Kornafel KL, Carmina E, Shoupe D, Stanczyk FZ and Lobo RA: Corticotropin-releasing factor decreases fasting insulin levels in patients with PCO. Presented at the 39<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.
194. Carmina E, Getzschein E and Lobo RA: Evidence for increased androsterone metabolism in nonhyperandrogenic acne. Presented at the 39<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.
195. Ditkoff EC, Fruzzetti F, Chang L, Stanczyk FZ and Lobo RA: Ovarian influence on adrenal androgen sensitivity and secretion in PCO. Presented at the 39<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.
196. Price T, Carr B, Dupulis R, Stanczyk F and Lobo R: Multiple dose pharmacokinetics of  
a 35 µg ethinyl estradiol, 1 mg norethindrone oral contraceptive in women with chronic renal failure on peritoneal dialysis. Presented at the 39<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.
197. Miles RA, Lobo RA, Paulson RJ and Sauer MV: The use of testolactone to prevent ovarian hyperstimulation syndrome (OHSS) after gonadotropin therapy. Presented at the 39<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.
198. Carmina E, Koyma T, Chang L, Stanczyk FZ and Lobo RA: Ethnic variability in polycystic ovary syndrome (PCO): Insight into pathophysiology. Presented at the 39<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.
199. Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: Toward ultimate in vitro fertilization (IVF): Addition of the GnRH antagonist Nal-Glu and pure FSH to unstimulated IVF cycles. Presented at the 39<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.

200. Miles RA, Lobo RA, Gentzchein E, Moyer D, Presser MF, Koopersmith T, Paulson RJ and Sauer MV: Assessing the pharmacodynamic properties of exogenously administered progesterone: A comparison of micronized vaginal delivery to intramuscular routes. Presented at the 40<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 8-12, 1992, Indian Wells, California.
201. Miles RA, Gentzschein E, Goedert L, Stanczyk FZ and Lobo RA: Assessment of androgen suppression using androstenedione gel. Presented at the 40<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 8-12, 1992, Indian Wells, California.
202. Lindheim SR, Ditkoff EC, Presser SC, Vijod MA, Stanczyk FZ and Lobo RA: A biomodal effect of estrogen on insulin resistance in postmenopausal women and a potential attenuating effect of progestin. Presented at the 40<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 8-12, 1992, Indian Wells, California.
203. Lindheim SR, Legro RS, Chang L, Vijod MA, Shoupe D, Stanczyk FZ and Lobo RA; Enhanced reactivity to induced behavioral stress in polycystic ovary syndrome. Presented at the 40<sup>th</sup> Annual Meeting of the Pacific Coast Fertility Society, April 8-12, 1992, Indian Wells, California.
204. Carmina E, Janni A and Lobo RA: Physiologic hormonal replacement enhances the effect of GnRH-agonist treatment for hirsutism in patients with ovarian hyperandrogenism. Presented at the 74<sup>th</sup> Annual Meeting of The Endocrine Society, June 24-27, 1992, San Antonio, Texas.
205. Stanczyk FZ, Carmina E, Gentzschein E and Lobo RA: Specific elevations in C19 conjugate levels in hyperandrogenic women with hirsutism. Presented at the 74<sup>th</sup> Annual Meeting of The Endocrine Society, June 24-27, 1992, San Antonio, Texas.
206. Cassidenti DL, Ary BA and Lobo RA: Leuprolide acetate (LA) followed by clomiphene citrate (CC) induces ovulation in clomiphene resistant patients with polycystic ovary syndrome (PCO). Presented at the 48<sup>th</sup> Annual Meeting of The American Fertility Society, October 31-November 5, 1992, New Orleans, Louisiana.
207. Lindheim SR, Legro RS, Vijod MA, Stanczyk FZ and Lobo RA: Does racial background influence the effect of estrogens on the hormonal response to stress? Presented at the 48<sup>th</sup> Annual Meeting of The American Fertility Society, October 31-November 5, 1992, New Orleans, Louisiana.
208. Lindheim SR, Kades WW, Wassilv VM, Chang L, Kojima T, Saad MF and Lobo RA: Effects of IGF-1 and insulin in PCO. Presented at the 40<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1991, Toronto, Ontario, Canada.
209. Carmina E, Gentzschein E, Stanczyk FZ and Lobo RA: Substrate dependency of C19

- conjugates in hyperandrogenic women and the influence of adrenal androgen. Presented at the 40<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.
210. Lindheim SR, Sauer MV, Francis MM, Macaso TM, Lobo RA and Paulson RJ; Elevated early follicular phase FSH levels in unstimulated cycles: Effects on follicular dynamics and oocyte maturation. Presented at the 40<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.
  211. Duffy DM, Lobo RA, Paulson RJ and Sauer MV: Follicular and endometrial response to fixed dose regimens of estrogen and progesterone among cycling women preparing for oocyte donation. Presented at the 40<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.
  212. Stanczyk FZ, Gentzschein E, Kojima T, Ary BA, Ziogas A and Lobo RA: Comparison of urinary unconjugated progesterone with urinary pregnanediol glucuronide as a marker of luteal activity. Presented at the 40<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.
  213. Legro RS, Carmina E, Gentzschein E, Stanczyk FZ and Lobo RA: Evidence for decreased androgen glucuronidation in balding men and androgenic alopecia. Presented at the 40<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.
  214. Lindheim SR, Buchanan TA, Duffy DM, Vijod MA, Kojima T and Lobo RA: Estimates of insulin resistance in postmenopausal women: Comparison of the ITT and the IVGTT. Presented at the 40<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.
  215. Legro RS, Shahbarami B, Lobo RA and Kovacs B: Size polymorphisms of the androgen receptor among female Hispanics and correlation with peripheral hyperandrogenism. Presented at the 40<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.
  216. Legro RS, Muhleman D, Comings D, Lobo RA and Kovacs B: D3 receptor polymorphisms associated with oligo-ovulation among female Hispanics. Presented at the 40<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.
  217. Lindheim SR, Legro RS, Wong IL, Tran DQ, Chang L and Lobo RA: Attenuating effects of progestin on adaptation to behavioral stress in postmenopausal women. Presented at the 40<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.
  218. Wong IL, Chang L, Spahn M-A F, Lindheim SR, Stanczyk FZ and Lobo RA; Characterization of the ovarian steroidogenic abnormality in PCO. Presented at the 40<sup>th</sup>

Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.

219. Legro RS, Blanche P, Krauss RM and Lobo RA: Alterations in atherogenic lipoproteins among hyperandrogenic women: Influence of insulin and genetic factors. Presented at the 40th Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.
220. Ary BA, Stanczyk FZ, Fahy MA and Lobo RA: 6-sulfatoxymelatonin levels in ovulatory women. Presented at the 40th Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.
221. Lindheim SR, Kojima T, Duffy DM, Vijod MA, Stanczyk FZ and Lobo RA: Insulin sensitivity is decreased in normal women by doses of ethinyl estradiol used in oral contraceptives. Presented at the 41st Annual Meeting of the Pacific Coast Fertility Society, April 14-18, 1993, Indian Wells, California.
222. Lindheim SR, Duffy DM, Kojima T, Vijod MA, Stanczyk FZ and Lobo RA: The route of administration influences the effect of estrogen on insulin sensitivity in postmenopausal women. Presented at the 41st Annual Meeting of the Pacific Coast Fertility Society, April 14-18, 1993, Indian Wells, California.
223. Lindheim SR, Sauer MV, Francis MM, Macaso TM, Lobo RA and Paulson RJ: In vitro fertilization (IVF) in unstimulated cycles: Utility of a midcycle FSH boost in addition to HCG for timing of follicle aspiration. Presented at the 41st Annual Meeting of the Pacific Coast Fertility Society, April 14-18, 1993, Indian Wells, California.
224. Carmina E and Lobo RA: Ovarian suppression reduces clinical and endocrine expression of late onset congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. Presented at the 75th Annual Meeting of The Endocrine Society, June 9-12, 1993, Las Vegas, Nevada.
225. Morris RS, Carmina E, Vijod MA, Stanczyk FZ and Lobo RA: Alterations in the sensitivity of serum IGF-1 and IGF-BP3 to octreotide in polycystic ovary syndrome (PCO). Presented at the 75th Annual Meeting of The Endocrine Society, June 9-12, 1993, Las Vegas, Nevada.
226. Ary BA, Chang L, Gentzschein E, Vijod M, Stanczyk FZ and Lobo RA: Comparison of GRF and clonidine as probes for the GH axis in normal and clomiphene resistant women with PCO. Presented at the conjoint meeting of The American Fertility Society and The Canadian Fertility and Andrology Society, October 9-14, 1993, Montreal, Quebec, Canada.
227. Duffy DM, Lindheim SR, Ary BA, Saad M, Vijod MA, Chang L and Lobo RA: The effects of growth hormone releasing factor (GRF) and insulin-like growth factor-1 (IGF-

- 1) on folliculogenesis in normal women. Presented at the conjoint meeting of The American Fertility Society and The Canadian Fertility and Andrology Society, October 9-14, 1993, Montreal, Quebec, Canada.
228. Morris RS, Duffy DM, Lindheim SR, Gentzschein E, Spahn M-A, Chang L, Espinoza TB, Anderson PW and Lobo RA: Angiotensin converting enzyme (ACE) inhibition during the normal menstrual cycle. Presented at the conjoint meeting of The American Fertility Society and The Canadian Fertility and Andrology Society, October 9-14, 1993, Montreal, Quebec, Canada.
  229. Lindheim SR, Legro RS, Morris RS, Lobo RA, Paulson RJ and Sauer MV: Altered stress responses in women undergoing in vitro fertilization and in recipients of oocyte donation. Presented at the conjoint meeting of The American Fertility Society and The Canadian Fertility and Andrology Society, October 9-14, 1993, Montreal, Quebec, Canada.
  230. Morris RS, Wong IL, Hatch IE, Paulson RJ and Lobo RA: Prerenin is elevated in PCO and may reflect hyperandrogenism. Presented at the 41<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 22-26, 1994, Chicago, Illinois.
  231. Wilcox JG, Morris RS, Gentzschein E, Stanczyk FZ and Lobo RA: The biological effects of  $17\alpha$ -dihydroequilin sulfate and its possible modulation of hepatic production. Presented at the 41<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 22-26, 1994, Chicago, and Illinois.
  232. Wong IL, Morris RS, Chang L, Spahn MA, Stanczyk FZ and Lobo RA: A prospective randomized trial comparing finasteride to spironolactone in the treatment of hirsute women. Presented at the 41<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 22-26, 1994, Chicago, Illinois.
  233. Duffy DM, Legro RS, Stanczyk FZ and Lobo RA: Comparisons between dihydrotestosterone (DHT) metabolism in blood and skin in men, women and polycystic ovary syndrome. Presented at the 41<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 22-26, 1994, Chicago, Illinois.
  234. Carmina E, Stanczyk FZ, Morris RS, Vijod MA, Lee PDK, Savjani G and Lobo RA: Altered regulation of IGFBP-1 and BP-3 in patients with PCO. Presented at the 41<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 22-26, 1994, Chicago, Illinois.
  235. Carmina E, Chang L, Gonzalez F and Lobo RA: Does the ovary explain elevated levels of DHEAS and  $11\beta$ -A in polycystic ovary syndrome (PCO)? Presented at the 41<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 22-26, 1994, Chicago, Illinois.

236. Hatch IE, Carmina E, Vijod MA, Gentschein E, Stanczyk FZ and Lobo RA: Inhibition of the IGF axis and 5-alpha reductase activity by 13-cis retinoic acid in normal women. Presented at the 41<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 22-26, 1994, Chicago, Illinois.
237. Wong IL, Morris RS, Paulson RJ, Lobo RA and Sauer MV: Isolated polycystic morphology in ovum donors predicts response to controlled hyperstimulation. Presented at the 41<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 22-26, 1994, Chicago, Illinois.
238. Morris RS, Wong IL, Lobo RA and Paulson RJ; Angiotensin converting enzyme (ACE) inhibition for the prevention of OHSS in rabbits: A randomized, prospective, double blinded trial. Presented at the 41<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 22-26, 1994, Chicago, Illinois.
239. Legro RS, Wong IL, Paulson RJ, Lobo RA and Sauer MV: Uterine aging does not adversely affect endometrial receptivity to embryo implantation in recipients of oocyte donation. Presented at the 41<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 22-26, 1994, Chicago, Illinois.
240. Legro RS, Wong IL, Paulson RJ, Lobo RA and Sauer MV: The natural history of multiple implantation following oocyte donation: A frequent but inefficient event. Presented at the 41<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 22-26, 1994, Chicago, Illinois.
241. Gonzalez F, Chang L, Horab T and Lobo RA: Further assessment of the role of ovarian steroids in the development of adrenal dysfunction. Presented at the 41<sup>st</sup> Annual Meeting of the Society for Gynecologic Investigation, March 22-26, 1994, Chicago, Illinois.
242. Hatch IE, Carmina E, Stanczyk FZ and Lobo RA; Serum AoG is a useful marker for the treatment of acne in normoandrogenic women. Presented at the 42<sup>nd</sup> Annual Meeting of the Pacific Coast Fertility Society, April 20-24, 1994, Indian Wells, California.
243. Duffy DM, Koch C, Gentschein E, Stanczyk FZ, Paulson RJ and Lobo RA: A re-evaluation of the importance of luteinizing hormone (LH) for follicle growth and oocyte maturity. Presented at the 42<sup>nd</sup> Annual Meeting of the Pacific Coast Fertility Society, April 20-24, 1994, Indian Wells, California.
244. Duffy DM, Bass D, Stanczyk FZ, Gentschein E and Lobo RA: The single FSH value: Evaluation of assay method, time interval, and operator differences. Presented at the 42<sup>nd</sup> Annual Meeting of the Pacific Coast Fertility Society, April, 20-24, 1994, Indian Wells, CA.



245. Morris RS, Wong IL, Gentszchein E, Sauer MV, Lobo RA and Paulson RJ: Angiotensin converting enzyme (ACE) inhibition for the prevention of ovarian hyperstimulation syndrome (OHSS): A randomized, prospective, placebo controlled, double blind trial. Presented at the 42<sup>nd</sup> Annual Meeting of the Pacific Coast Fertility Society, April 20-24, 1994, Indian Wells, California.
246. Morris RS, Wong IL, Sauer MV, Lobo RA and Paulson RJ: Predictive value of serum estradiol ( $E_2$ ) levels and oocyte number in the prediction of severe ovarian hyperstimulation. Presented at the 42<sup>nd</sup> Annual Meeting of the Pacific Coast Fertility Society, April 20-24, 1994, Indian Wells, California.
247. Carmina E, Stanczyk FZ, Gentszchein E and Lobo RA: Time-dependent changes in serum  $3\alpha$ -androstenediol glucuronide ( $3\alpha$ -diol G) correlate with hirsutism scores after ovarian suppression. Presented at the 76<sup>th</sup> Annual Meeting of The Endocrine Society, June 15-18, 1994, Anaheim, California.
247. Stanczyk FZ, Skinner EC, Spahn MF, Chang L, Mertes S, Ross R and Lobo RA; Effect of finasteride on serum unconjugated and conjugated androgen levels in men with prostate cancer. Presented at the 76<sup>th</sup> Annual Meeting of The Endocrine Society, June 15-18, 1994, Anaheim, California.
248. James WM, Morris RS, Gentszchein E, Carmina E and Lobo RA: The effects of octreotide on the adrenal response to corticotropin releasing factor (CRF) in polycystic ovary syndrome (PCO). Presented at the 50<sup>th</sup> Annual Meeting of The American Fertility Society, November 5-10, 1994, San Antonio, Texas.
250. Duffy DM, Chang L, Gentszchein E and Lobo RA: The use of corticotropin-releasing factor (CRF) to identify the mechanism of oral contraceptive (OC) induced adrenal suppression. Presented at the 50<sup>th</sup> Annual Meeting of The American Fertility Society, November 5-10, 1994, San Antonio, Texas.
251. Wong IL, Morris RS, Koopersmith TB, and Lobo RA: The effect of finasteride on ovulation function in normal women. Presented at the 50<sup>th</sup> Annual Meeting of The American Fertility Society, November 5-10, 1994, San Antonio, Texas.
252. Wilcox JG, Hodis HN, Hwang J, Sevanian A, Stanczyk FZ and Lobo RA: The biological effects of individual estrogen components in conjugated equine estrogens (CEE) and their possible modulation of insulin resistance and oxidation of LDL. Presented at the 42<sup>nd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1995, Chicago, Illinois.
253. Paulson RJ, Sauer MV and Lobo RA: Luteal phase antiprogesterone administration improves endometrial receptivity in hyperstimulated cycles: A hypothesis. Presented at the 42<sup>nd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1995, Chicago, Illinois.

254. Gonzalez F, Chang L, Horab T, Stanczyk FZ, Crickard K and Lobo RA: Adrenal dysfunction in polycystic ovary syndrome (PCO) as assessed by physiologic and pharmacologic adrenal dynamic responses in the presence and absence of ovarian steroids Presented at the 42<sup>nd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1995, Chicago, Illinois.
255. Hatch IE, Spahn MA, Wilcox JG, Stanczyk FZ and Lobo RA: Opiate regulation of insulin sensitivity and the IGF-1 axis in polycystic ovary syndrome (PCO). Presented at the 42<sup>d</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1995, Chicago, Illinois.
256. Paulson RJ, Hatch I, Lobo RA and Sauer MV: Lack of decrease of efficiency of oocyte donation substantiates lack of an intrinsic endometrial defect in embryo implantation. Presented at the 42<sup>nd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1995, Chicago, Illinois.
257. Hendershott CM, Millar LK, Hindle WH, Moyer D, Lobo RA and Felix JC: Hormone levels and proliferative activity in breast tissue throughout the menstrual cycle. Presented at the 42<sup>nd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1995, Chicago, Illinois.
258. Thornton MH, Najmabadi S, Hatch IE, Acacio B and Lobo RA: Evaluation of inappropriate gonadotropin secretion in polycystic ovary syndrome. Presented at the 42<sup>nd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1995, Chicago, Illinois.
259. Fruzzetti F, Lobo RA, De Lorenzo D, Parrini D, Ricci C, Ferrara A and Genazzani AR: Comparisons between various antiandrogens in the treatment of hirsutism: Differences between androgen suppression and peripheral effects. Presented at the 42<sup>nd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1995, Chicago, Illinois.
260. Hatch IE, Nicoloff JT, Spencer CA and Lobo RA: The effect of 13-cis retinoic acid (13-CIS RA) in normal cycling women: An explanation for the diverse endocrine mediated effects of 13-CIS RA. Presented at the 42<sup>nd</sup> Annual meeting of the Society for Gynecologic Investigation, March 15-18, 1995, Chicago, Illinois.
261. Price T, Blauer K, Hansen M, Stanczyk F, Lobo R and Bates GW: Pharmacokinetics of sublingual vs oral administration of micronized 17 $\beta$ -estradiol. Presented at the 42<sup>nd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1995, Chicago, Illinois.

262. Carmina E, Lo Dico G, Lee P, Saviani G, Gentzschein E, Spahn MA, Stanczyk FZ and Lobo RA: Oral estrogen administration increases serum IGFBP-1 and reduces "free" IGF-1. Presented at the 42<sup>nd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1995, Chicago, Illinois.
263. Mezrow G, Koopersmith T, Shoupe D and Lobo RA: Estrogen replacement therapy using micronized vaginal progesterone. Presented at the 42<sup>nd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1995, Chicago, Illinois.
264. Paulson RJ, Hatch IE, Lobo RA and Sauer MV; Cumulative success rates after oocyte donation: Life table analysis. Presented at the IXth World Congress on In Vitro Fertilization and Assisted Reproduction, April 3-7, 1995, Vienna, Austria.
265. Hatch IE, Kim MK and Lobo RA: Glucose intolerance in polycystic ovary syndrome (PCOS): Occult findings and risks of pregnancy. Presented at the 43<sup>rd</sup> Annual Meeting of the Pacific Coast Fertility Society, April 26-30, 1995, San Diego, California.
266. Hatch IE, Sauer MV, Lobo RA and Paulson RJ: Embryo implantation after repetitive cycles of oocyte donation. Presented at the 43<sup>rd</sup> Annual Meeting of the Pacific Coast Fertility Society, April 26-30, 1995, San Diego, California.
267. Thornton MH, Carmina E, Sauer MV, Paulson RJ, Najmabadi S, Stanczyk FZ, Spahn M-A and Lobo RA: Ovarian production of IGF-BP1 and its role in women with polycystic ovaries. Presented at the 43<sup>rd</sup> Annual Meeting of the Pacific Coast Fertility Society, April 26-30, 1995, San Diego, California.
268. Wilcox JG, Hatch IE, Gentzschein EK, Stanczyk FZ and Lobo RA: Possible modulation of endothelin levels in postmenopausal women receiving oral versus non-oral hormone replacement therapy. Presented at the 43<sup>rd</sup> Annual Meeting of the Pacific Coast Fertility Society, April 26-30, 1995, San Diego, California.
269. Koopersmith TB, Sauer MV and Lobo RA: Programmed cycles for frozen embryo transfer: A simplified approach. Presented at the 43<sup>rd</sup> Annual Meeting of the Pacific Coast Fertility Society, April 26-30, 1995, San Diego, California.
270. Paulson RJ, Sauer MV and Lobo RA: Manipulation of the window of implantation in the human: A proposal. Presented at the 43<sup>rd</sup> Annual Meeting of the Pacific Coast Fertility Society, April 26-30, 1995, San Diego, California.
271. Adler MA and Lobo RA: Estrogen replacement therapy alters immune competence in postmenopausal women. Presented at the 43<sup>rd</sup> Annual Meeting of the Pacific Coast Fertility Society, April 26-30, 1995, San Diego, California.
272. Carmina E, Wong IL, Thornton MH, Stanczyk FZ, Paulson RJ, Sauer MV and Lobo RA: Androgen profiles of ovulatory women with polycystic appearing ovaries and alterations in serum IGF-BP1. Presented at the 77<sup>th</sup> Annual Meeting of The Endocrine

Society, June 14-17, 1995, Washington, D.C.

273. Stanczyk FZ, Carmina E, Skinner EC, Mertes S, Spahn MF, Lee PDK, Savjani G, Ross RK and Lobo RA: Influence of androgen, specifically of 5-reductase activity, but not age on serum IGFBP-1 levels in men. Presented at the 77<sup>th</sup> Annual Meeting of The Endocrine Society, June 14-17, 1995, Washington, D.C.
274. Carmina E and Lobo RA: GnRH-agonist therapy for hirsutism is as effective as high dose cyproterone acetate but results in a longer remission: Presented at the 51<sup>st</sup> Annual Meeting of the American Society for Reproductive Medicine, October 7-12, 1995, Seattle, Washington.
275. Thornton MH, Wang C-Y, Spahn M-A, Stanczyk FZ and Lobo RA: Changes in the IGF-1 axis with clomiphene citrate in ovulatory women with PCOS. Presented at the 51<sup>st</sup> Annual Meeting of the American Society for Reproductive Medicine, October 7-12, 1995, Seattle, Washington.
276. Graczykowski JW, Chang L, Stanczyk FZ and Lobo RA: Does chronic estrogen administration influence pharmacokinetic profiles and does progestin attenuate estrogen bio-availability? Presented at the 51<sup>st</sup> Annual Meeting of the American Society for Reproductive Medicine, October 7-12, 1995, Seattle, Washington.
277. Koopersmith TB, Gray D, Horowitz D and Lobo RA: Modulation of cytokine and immunoglobulin levels by sex steroids in women. Presented at the 51<sup>st</sup> Annual Meeting of the American Society for Reproductive Medicine, October 7-12, 1995, Seattle, Washington.
278. Graczykowski JW, Wang C-Y, Stanczyk FZ and Lobo RA. The effect of medroxy-progesterone acetate on insulin sensitivity in postmenopausal women on estrogen replacement therapy. Presented at the 43<sup>rd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1996, Philadelphia, Pennsylvania.
279. Wilcox JG, Hwang J, Gentzschin EK, Hodis HN, Sevanian A, Stanczyk FZ and Lobo RA. Effects of combined estrogen and progestin therapy in postmenopausal women on endothelin levels and oxidation of LDL. Presented at the 43<sup>rd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1996. Philadelphia, Pennsylvania.
280. Wang C-Y, Stanczyk FZ and Lobo RA. Quantitative measurement of mRNAs encoding type I and type II 5 $\alpha$ -reductase genes in hirsute and non-hirsute women. Presented the 43<sup>rd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1996, Philadelphia, Pennsylvania.

281. Carmina E and Lobo RA. Baseline characteristics of hyperandrogenic women influencing the choice of therapy for hirsutism and whether the agent influences the length of remission. Presented at the 43<sup>rd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1996, Philadelphia, Pennsylvania.
282. Najmabadi S, Thornton MH, Acacio BD and Lobo RA. An assessment of differences in luteinizing hormone (LH) dynamics in patients with polycystic ovary syndrome (PCOS) who have normal or elevated LH. Presented at the 43<sup>rd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1996, Philadelphia, Pennsylvania.
283. Wilcox JG, Najmabadi S, Gentzchein EK, Acacio BD, Stanczyk FZ and Lobo RA. Metformin improves the hormonal profiles of patients with polycystic ovary syndrome. Presented at the 43<sup>rd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1996, Philadelphia, Pennsylvania.
284. Wang C-Y, Jacob C, Graczykowski JW, Kolb BA, Stanczyk FZ, Paulson RJ, Reichardt JKV, Tao I, Gentzchein E and Lobo RA. Length polymorphism of the type II 5 $\alpha$ -reductase gene is associated with hirsutism. Presented at the 43<sup>rd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1996, Philadelphia, Pennsylvania.
285. Najmabadi S, Acacio BD, Thornton MH, Krauss RM and Lobo RA. Effects of transdermal estradiol on serum lipids/lipoproteins and glucose tolerance in postmenopausal hypercholesterolemic women. Presented at the 43<sup>rd</sup> Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1996, Philadelphia, Pennsylvania.
286. Hwang J, Wilcox JG, Hodis HN, Lobo RA, Sevanian A: Inhibition of low density lipoprotein oxidation in postmenopausal women receiving combined estrogen therapy. Presented at the American Heart Association, 69th Scientific Sessions, 1996.
287. Wang C-Y, Carmina E, Chang L, Wong IL, Stanczyk FZ, Lobo RA: Effect of finasteride on circulating levels of insulin-like growth factors (IGFs), testosterone, dihydrotestosterone, and their binding proteins in hirsute women. Presented at the 44<sup>th</sup> Annual Meeting of The Pacific Coast Fertility Society, April 17-21, 1996.
288. Chang PL, Lindheim SR, Carmina E, Vidali A, Ferin M, Sauer MV, Lobo RA: Do normal ovulatory women of normal weight who have polycystic ovaries have features of polycystic ovary syndrome. Presented at 44<sup>th</sup> Annual Meeting of the Society of Gynecologic Investigation, San Diego, March 19-22, 1997, Abs. # 46.
289. Carmina E, Gonzalez F, Ashok M, Stanczyk FZ, Lobo RA: Influence of insulin and components of the IGF-axis on adrenal hyperandrogenism in PCOS. Presented at 44<sup>th</sup> Annual Meeting of the Society of Gynecologic Investigation, San Diego, March 19-22, 1997, Abs. # 176.
290. Carmina E, Gonzalez F, Vidali A, Ferin M and Lobo RA: High leptin and low IGF-

BP1 circulating levels in a subgroup of normoweight women with polycystic ovary syndrome (PCOS). Presented at the 79th Annual Meeting of The Endocrine Society, June 11- 14, 1997.

291. Lindheim SR, Chang PL, Ferin M, Lobo RA and Sauer MV: The utility of serum progesterone and inhibin A in monitoring unstimulated IVF-ET cycles. 53<sup>rd</sup> Annual Meeting of the American Society for Reproductive Medicine, October 18-22, 1997, Cincinnati, Ohio.
292. Lobo RA: Diagnostic dilemmas in PCOS. ASRM symposia Highlights on New Perspectives in Polycystic Ovary Syndrome. 53<sup>rd</sup> Annual Meeting of the American Society for Reproductive Medicine, October 18-22, 1997, Cincinnati, Ohio. Medical Association Communications and American Society for Reproductive Medicine, 1997.
293. Carmina E, Ferin M. and Lobo R: Evidence that adrenal androgens inhibit and insulin stimulates serum leptin concentrations in women with polycystic ovaries. Presented at the 45<sup>th</sup> Annual Meeting of the Society of Gynecologic Investigation, Atlanta, Georgia, March 11-14, 1998.
294. Carmina E, Lobo R: Prevalence and characteristics of ovulation occurring in hyperandrogenic women. Presented at the 45<sup>th</sup> Annual Meeting of the Society of Gynecologic Investigation, Atlanta, Georgia, March 11-14, 1998.
295. Lobo RA: Diagnostic Dilemmas in PCOS. New Perspective in Polycystic Ovary Syndrome. At a session held during ASRM's 53<sup>rd</sup> Annual Meeting, October 18-22, 1997, in Cincinnati, Ohio. American Society for Reproductive Medicine (ASRM). 1997 Annual Meeting - Symposia Highlights. Medical Association Communications and the American Society for Reproductive Medicine, 1998.
296. Lobo RA: How to Determine the Role of Androgens. North American Menopause Society (NAMS) 9<sup>th</sup> Annual Meeting, September 16, 1998.
297. Lobo RA. Managing physiological changes of induced menopause. Satellite Symposium on Clinical Management of Women Following Induced Menopause". The 9<sup>th</sup> Annual Meeting of The American Menopause Society, September 16-19, 1998.
298. Lindheim SR, Sauer MC, Carmina E, Zimmerman R, Chang, P and Lobo RA. Circulating leptin during ovulation induction has no relationship to adiposity and ovarian morphology. The 46<sup>th</sup> Annual Meeting of the Society of Gynecologic Investigation, Atlanta, Georgia, March 10-13, 1999.
299. Chang P, Lindheim SR, Ferin M, Carmina E, Lowry C, Sauer MV and Lobo RA. Normal ovulatory women with polycystic ovaries have hyperandrogenic pituitary-ovarian responses to gonadotropin releasing hormone-agonist (GnRH-a) testing. The 46<sup>th</sup> Annual

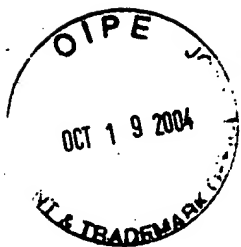
Meeting of the Society of Gynecologic Investigation, Atlanta, Georgia, March 10-13, 1999.

300. Wang C-Y, Stanczyk FZ, Zheng WX, Felix J and Lobo RA. Localization of human type I and type II 5 $\alpha$ -reductase mRNAs in genital skin of hirsute and non-hirsute women. 46<sup>th</sup> Annual Meeting of the Society of Gynecologic Investigation, Atlanta, Georgia, March 10-13, 1999 (A376).
301. Carmina E and Lobo RA. The association of hyperandrogenism and ovulatory status with insulin resistance and lipoprotein levels in women. SGI 2000- A Millennial Milestone in Reproductive Sciences: Celebrating the Promise. 47<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, Chicago, Illinois, March 23-26, 2000 (A923).
302. Carmina E, Lippman J, Godwin A and Lobo RA. Androsterone glucuronide is a useful marker for acne lesions and correlates with the effectiveness of treatment. SGI 2000- A Millennial Milestone in Reproductive Sciences: Celebrating the Promise. 47<sup>th</sup> Annual Meeting of the Society for Gynecologic Investigation, Chicago, IL, March 23-26, 2000. (A441).
303. Carmina E, Lobo RA. The prevalence and clinical importance of diagnosing PCOS in ovulatory hirsute women. ENDO 2000 The Endocrine Society 82<sup>nd</sup> Annual Meeting. Toronto, Ontario, Canada, June 21-24, 2000 (A2334).
304. Lobo, RA. Physiology of Androgens in Women. Androgens in Women: Physiology, Deficiency, and Emerging Therapeutic Potentials. CMES Ancillary Symposium. The Endocrine Society Annual Meeting. ENDO 2000, Toronto, Canada, June 22, 2000.
305. Lobo RA. Estrogen agonists and antagonists. The Annual Meeting of the ESHRE, Bologna (Italy), June 25-28, 2000.
306. Lobo RA. Bone metabolism and progestin hormonal contraception. New two-rod levonorgestrel implants for contraception. Leiras Oy, Jadelle Symposium at the XVI FIGO World Congress of Gynecology and Obstetrics in Washington, September 7, 2000. The Parthenon Publishing Group, International Publishers in Medicine, Science & Technology, Carnforth, Lancs, United Kingdom.
307. Archer DA, Lobo RA, Utian WH, Pickar JH. Improved amenorrhea, favorable vasomotor and lipid effects, and endometrial safety with lower doses of conjugated estrogens (CE) and medroxyprogesterone acetate (MPA). "Late Breaking News," American Society for Reproductive Medicine (ASRM), 2000.
308. Hodis HN, Mack WJ, Lobo RA, Shoupe D, Sevanian A, Mahrer PR, Selzer RH, Liu CR, Liu CH, Azen SP. Estrogen in the prevention of atherosclerosis trial. Circulation

102:II. 837 (Abstract).

309. Carmina E, Lobo RA. A comparison of the relative efficacy of antiandrogen therapy for acne and alopecia in hyperandrogenic women. The 48<sup>th</sup> Annual Society for Gynecological Investigation (SGI) Meeting, March 15, 2001 (A151).
310. Carmina E, Legro R, Stamets K, Lowell J, Lobo RA. The influence of diet on the obesity and metabolic alterations in polycystic ovary syndrome. The Endocrine Society June 2001 Annual Meeting, (A37801).
311. Lobo RA, Bush T, Carr BR, Picar JH. Effects of lower doses of conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) on plasma lipids. The American Society for Reproductive Medicine (ASRM) meeting 2001 (A1186).
312. Carmina, E, Longo A, Lobo RA. Does ovarian blood flow distinguish between ovulatory and anovulatory patients with polycystic ovary syndrome. The Endocrine Society's 84<sup>th</sup> Annual Meeting. Abs. # 851188, 2002.
313. Ruman J, Rennaer R, Chung W, Thornton M, Zimmermann R, Sauer MV, Lobo RA and Zeitoun K. The Endocrine Society's 84<sup>th</sup> Annual Meeting. Abs. # 853627, 2002.
314. Carmina E, Lobo RA. Does metformin induce ovulation in normoandrogenic anovulatory women? The Endocrine Society's 85<sup>th</sup> Annual Meeting, June 19-22, 2003. Abs. # 851730, 2003.





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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S) : PICKAR, J., DEY M.  
SERIAL NO. : 09/808,878  
FILED : March 15, 2001  
TITLE : HORMONE REPLACEMENT THERAPY  
ART UNIT : 1617  
EXAMINER : M. Bahar

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

SECOND DECLARATION UNDER 37 C.F.R. § 1.132

SIR:

I, ROGERIO A. LOBO, M.D., declare as follows:

1. The statements made in my Declaration Under 37 C.F.R. § 1.132 submitted on April 1, 2003 are incorporated herein, including information regarding my background and qualifications and my curriculum vitae attached as Exhibit A thereto.
2. For the past 20 years, the dosage of 0.625 mg CEE has been accepted as the minimum dosage of estrogen necessary to relieve the symptoms of menopause, including hot flashes and bone loss. (See, e.g., Sobel NB, Obstetrics and Gynecology Clinics of North America, 21:299-319 (1994) (describing 0.625 mg as the standard dose of conjugated estrogen) (Ex. A hereto); Kronenberg F, Chapter 9: Hot Flashes, in Rogerio A. Lobo, ed., Treatment of the Postmenopausal Woman: Basic and Clinical Aspects, New York, NY: Raven Pres, at 109 (1994)) ("The most commonly used regimen for treating hot flashes in the United States is 0.625 to 1.25 mg of oral conjugated equine estrogen (Premarin)") (Ex. B hereto). The dosage of 2.5 mg of MPA has

been recognized as the minimum amount needed to oppose 0.625 mg CEE and protect the endometrium. This combination of 0.625 mg CEE plus 2.5 mg MPA daily has been the most commonly prescribed combination estrogen-progestin hormone replacement therapy regimen in the United States. (See, e.g., Kreling D, et al., Prescription Drug Trends: A Chartbook Update, Menlo Park, CA: Kaiser Family Foundation, at 51 (2000)) (Ex. C hereto).

3. The preferred dosage of CEE that Plunkett discloses is 0.600 mg CEE. Page 9 of Applicants' application compares the claimed invention to a combination using 0.625 mg CEE. The difference between the dosages of 0.600 mg CEE and 0.625 mg CEE is not a meaningful difference when compared to Applicants' invention. For purposes of treating or inhibiting vasomotor symptoms, one skilled in the art would consider a daily dosage of 0.600 mg CEE to be clinically equivalent to a dosage of 0.625 mg CEE. Therefore, Applicants provided comparative results of its claimed invention with the preferred dosages of MPA and CEE that Plunkett discloses.

4. The results on page 9 of Applicants' application describe some of the results obtained in the Women's Health, Osteoporosis, Progestin, Estrogen study ("H.O.P.E. study"). Relief of vasomotor symptoms was analyzed in patients who experienced at least an average of 7 to 8 moderate-to-severe hot flushes per day during the 7-day period just prior to the initiation of treatment in this study. The results on page 9 reflect the results of 4 of the 8 regimens used in the H.O.P.E. study administered daily: (1) 0.625 mg CEE plus 2.5 mg MPA ("PREMPRO"); (2) 0.45 mg CEE plus 1.5 mg MPA; (3) 0.3 mg CEE plus 1.5 mg MPA; and (4) a placebo. The first table on page 9 shows the mean number of hot flushes. The second table shows the mean daily severity of the flushes. These results are also shown in Figures 1 and 2.

5. The results on page 9 of Applicants' application show that all doses of CEE plus MPA reduced the mean number and mean severity of hot flushes experienced by the women in the clinical study compared with taking placebo. The mean daily number and mean severity of hot

flushes in the lower dosage groups were not significantly different than the mean number and mean severity of the much higher and commercially available dose combination containing 0.625 mg CEE and 2.5 mg MPA. These results demonstrated that the combinations of 1.5 mg MPA with the lower doses, 0.45 or 0.30 mg, CEE, were as effective in rapidly reducing the number and severity of hot flushes to essentially the much higher and commercially available dose combination containing 0.625 mg CEE and 2.5 mg MPA.

6. The results on page 9 of Applicants' application were contrary to what would have been expected to those skilled in the art. The results surprisingly and unexpectedly demonstrated that all doses of CEE and MPA reduced the number and severity of hot flushes experienced by the women in this study compared with women taking placebo. It was unexpected that providing a daily dosage of 1.5 mg MPA in combination with the lower doses, 0.45 or 0.30 mg, CEE, rapidly reduced the number and severity of hot flushes to the same extent as the much higher and commercially available dose combination containing 0.625 mg CEE and 2.5 mg MPA.

7. The H.O.P.E. study demonstrated that dosages of CEE and MPA may be better than equivalent dosages of unopposed CEE for vasomotor symptom relief. Previous studies with various dosages of CEE showed no additive effect of MPA on vasomotor relief. (See Greendale et al., Obstetrics and Gynecology, 92:982-988 (1998)). Greendale et al. reported studies using the following regimens: (1) placebo; (2) 0.625 mg CEE daily; (3) 0.625 mg CEE daily plus 2.5 mg MPA daily; (4) 0.625 mg CEE daily plus 10 mg MPA for 12 days per month; and (5) 0.625 mg CEE daily plus 200 mg micronized progesterone for 12 days per month. Greendale et al. reported that there was "convincing evidence" that regimens using CEE plus MPA were not more effective than CEE alone against vasomotor symptoms. However, the H.O.P.E. study unexpectedly demonstrated that at the particular low dose of 1.5 mg, MPA may contribute vasomotor relief in combination with the lower dosages of 0.3 or 0.45 mg CEE. These results are

preliminary evidence that there is a therapeutic role for MPA beyond endometrial protection when lower dosages of CEE are used. The H.O.P.E. study surprisingly demonstrated that at these low doses MPA may contribute to ameliorating the vasomotor symptoms.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the patent or any reexamination certificate issued therefor.

Dated: \_\_\_\_\_

12/15/03

  
\_\_\_\_\_  
ROGERIO A. LOBO, M.D.

# OBSTETRICS AND GYNECOLOGY CLINICS OF NORTH AMERICA

Primary Care of the Mature Woman

VERONICA A. RAVNIKAR, MD, GUEST EDITOR

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VOLUME 21 • NUMBER 2 • JUNE 1994

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# PROGESTINS IN PREVENTIVE HORMONE THERAPY

Including Pharmacology of the New Progestins, Desogestrel, Norgestimate, and Gestodene: Are There Advantages?

Nancy B. Sobel, MD, PhD

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## HISTORY

The development and characterization of the synthetic progestins used in hormone replacement therapy (HRT) and contraception are an outgrowth of research on the hormonal control of reproduction conducted during the early to middle twentieth century. Progesterone was isolated from the corpus luteum of sows by Corner and Allen in the 1930s. Before this, progesterone had been synthesized commercially from plant (soy beans, yams) and animal (ox bile) sources. It was not until Marker successfully synthesized progesterone from the Mexican yam in the 1940s that large quantities of progesterone became available at a reasonable price. Natural steroids, however, are difficult to control. They are inactive when given orally and highly insoluble in plasma, and therefore, the search for orally active steroids was begun. Originally motivated by the synthesis of cortisone, chemists discovered the progestational activity of 19-norsteroids. In 1951, Djerassi<sup>15</sup> prepared a derivative of 19-nortosterone, norethisterone (known as norethindrone in the United States), which was the first highly effective, orally active progestogen for human use. In subsequent years, attention was focused principally on the potential of progestational agents to control abnormal bleeding, and then as a contraceptive agent, resulting in the first oral agent in the early 1960s.<sup>17, 26, 82</sup>

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From the Department of Gynecology, Lahey Clinic, Burlington; and Department of Gynecology, Massachusetts General Hospital, Boston, Massachusetts

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OBSTETRICS AND GYNECOLOGY CLINICS OF NORTH AMERICA

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## PROGESTIN STRUCTURE AND NOMENCLATURE

Steroid hormones are derivatives of cholesterol, a 27-carbon compound, and have a common chemical structure based on the 4-ring perhydrocyclopentane-phenanthrene molecule. This is composed of one 5-carbon and three 6-carbon rings lettered A through D and numbered counterclockwise (Fig. 1). The sex steroid hormones are divided into three main groups according to their number of carbon atoms: the 21 carbon (21C) pregnane nucleus, precursor for progestins (and corticoids); the 19C androgen series, based on the androstane nucleus; and 18C estrogen, from the estrane nucleus. Synthetic progestins are also classified into three groups: pregnanes, estranes, and gonanes.

Estranes and their derivatives, the gonanes, are employed predominantly in contraception, and all are derived from norethindrone. Because both groups are characterized by the absence of a methyl group between rings A and B (i.e., C19), they have been designated the 19-nortestosterone progestins or 19-norprogestins (Fig. 2). All the structures are similar, but the "minor" alterations in structure can lead to dramatic differences in biochemical activity. Estranes are characterized by the addition of an ethinyl group at position 17. Differences between estranes involve double-bond position (norethynodrel) and placement of acetate moieties (norethindrone acetate and ethynodiol diacetate). Norgestrel, the first gonane progestin, synthesized from norethindrone by Smith<sup>81</sup> in the early 1960s, is also included in this class.

The gonanes include norgestrel and its biologically active L-isomer, levonorgestrel (LNG). The gonanes are distinguished from the estranes by the addition of a methyl group at position C18 (Fig. 3). In the 1970s and 1980s, efforts were made to minimize the intrinsic androgenicity of the 19-norprogestins. This produced a new generation of progestins, the gonanes desogestrel (Organon, Org 2969), norgestimate (Ortho-Cilag, ORF 10131), and gestodene (Schering AG, SH T 546). Structurally, gestodene differs from LNG only by the presence of a double bond in the D ring between carbons 15 and 16. Desogestrel differs from these by the absence of a keto group at position 3. Norgestimate is LNG with an oxime group at C3 and an additional acetate group at C17.

Another group of progestins, the pregnanes, became available when it was discovered that acetylation of the 17-hydroxy group of 17-hydroxyprogesterone also produced oral potency. Pregnanes, C-21 progestins, are the class of progestins widely used for noncontraceptive applications such as HRT and the treatment of carcinoma. These include medroxyprogesterone acetate (MPA), megestrol acetate, chlormadione acetate, and cyproterone acetate. Each drug has substituents at the 17 and 6 positions. Interestingly, these agents were not used in oral contraceptives (OC) because early studies, later refuted, associated high doses with an increased incidence of carcinoma of the breast in beagle dogs. In fact, only one pregnane-containing OC, Provest, ever reached the US market.<sup>17</sup>

## PHARMACODYNAMICS AND SELECTIVITY

On ingestion, oral steroids are absorbed by the small intestines. From there, they are transported by means of the portal system to the liver where they may be modified and circulated systemically or eliminated by biliary excretion. This is referred to as the liver's presystemic or *first-pass* effect. From the gallbladder, molecules are returned to the small bowel, reabsorbed into the portal circulation, or excreted in the feces.<sup>63, 90</sup> Norgestrel does not undergo a first-pass effect,<sup>67</sup> although most other progestins do, resulting in variations in bioavailability among users.

*Text continued on page 305*

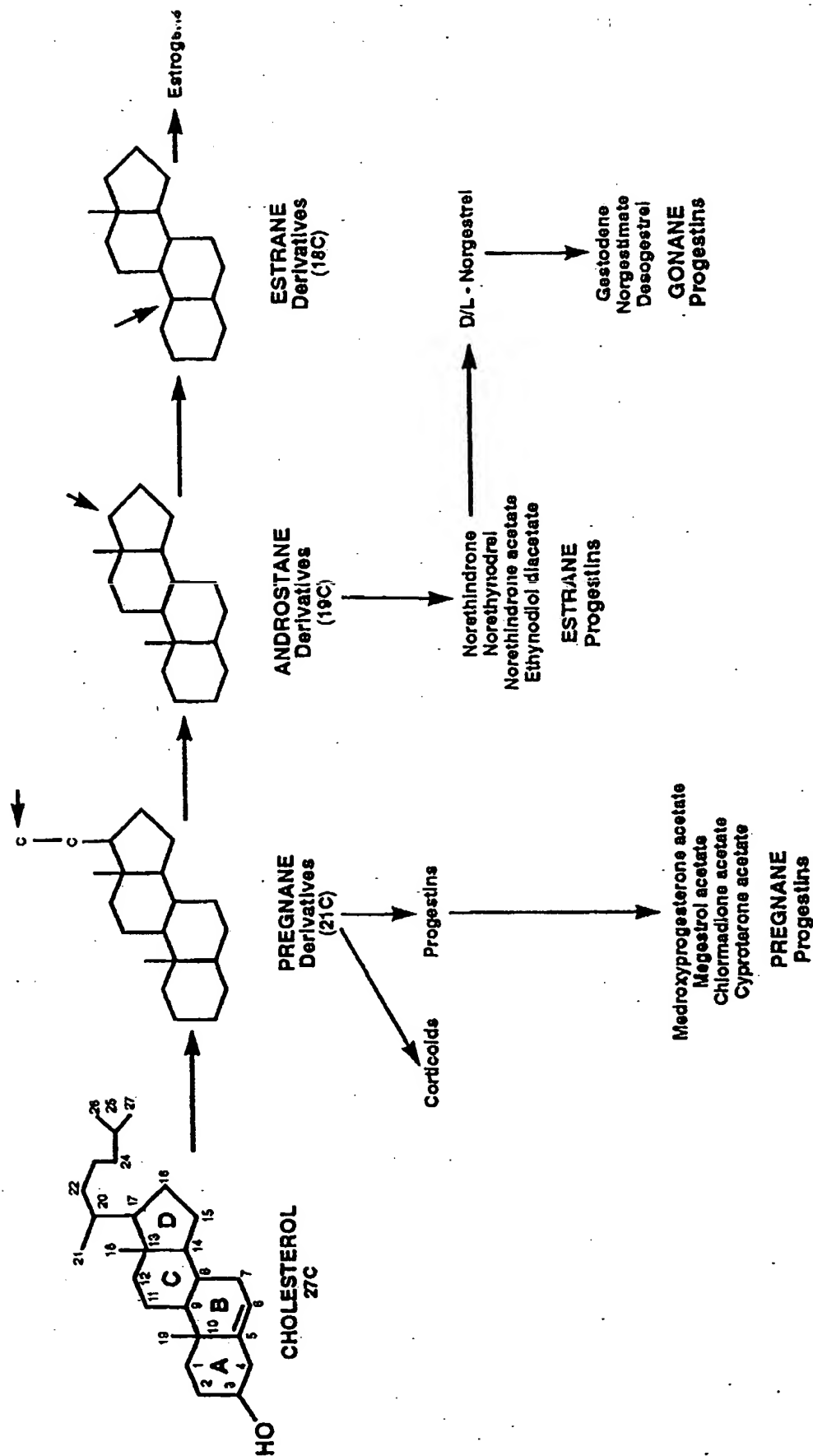


Figure 1. Relationship of synthetic progestins used in hormone replacement therapy.



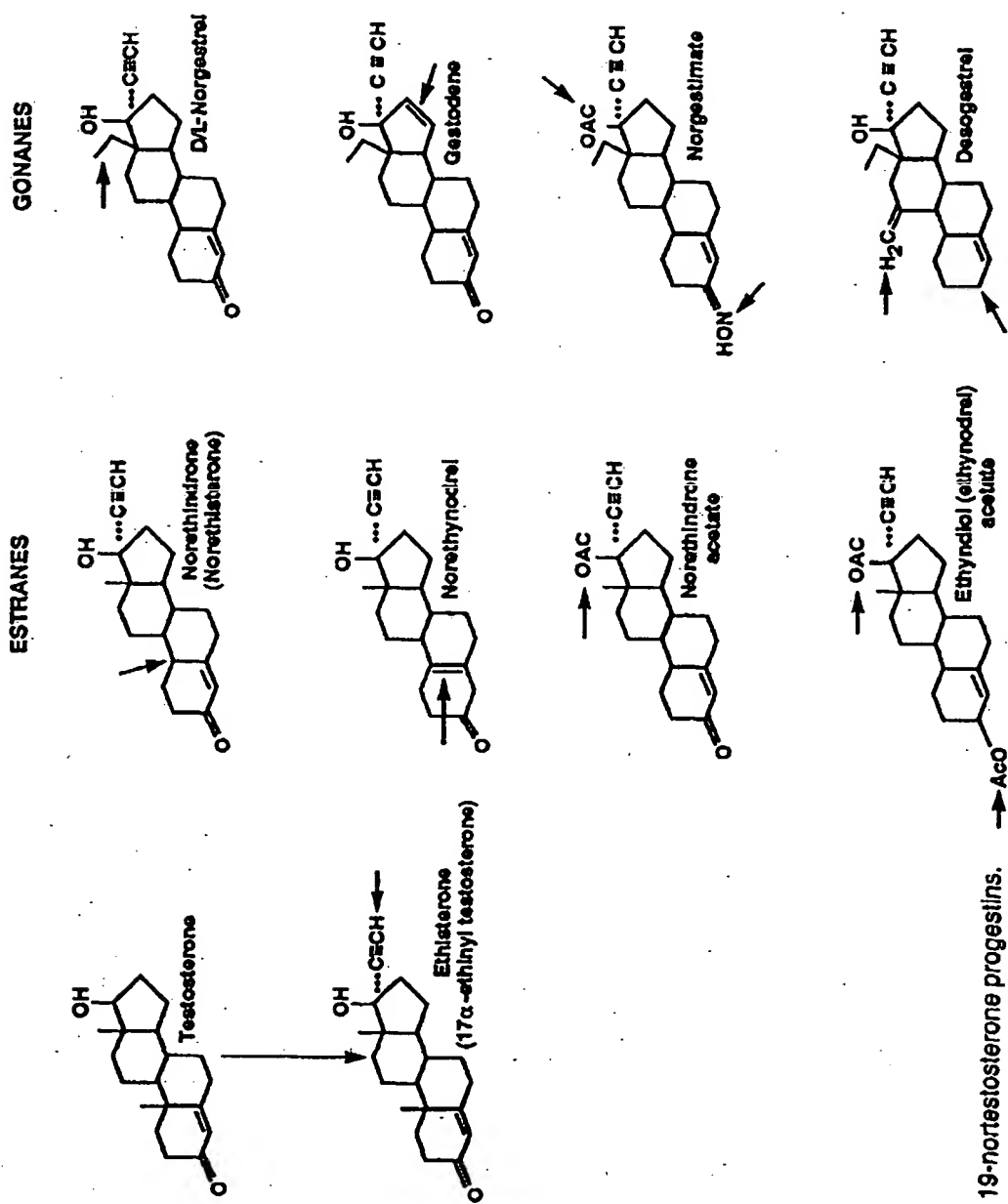


Figure 2. 19-nortestosterone progestins.

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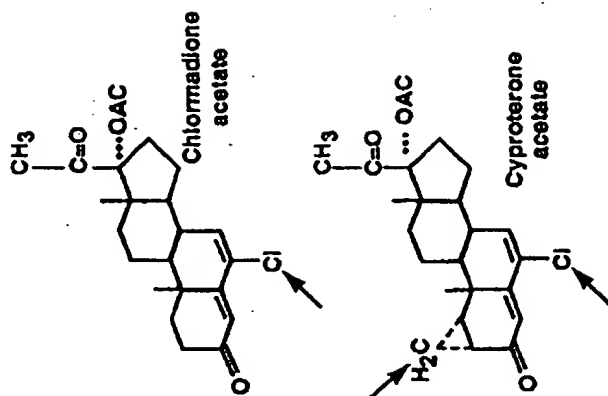
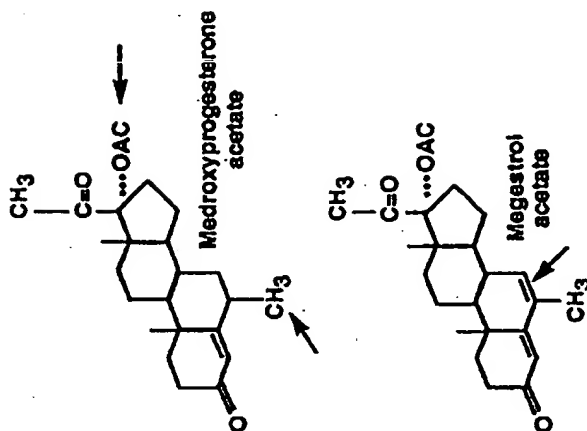
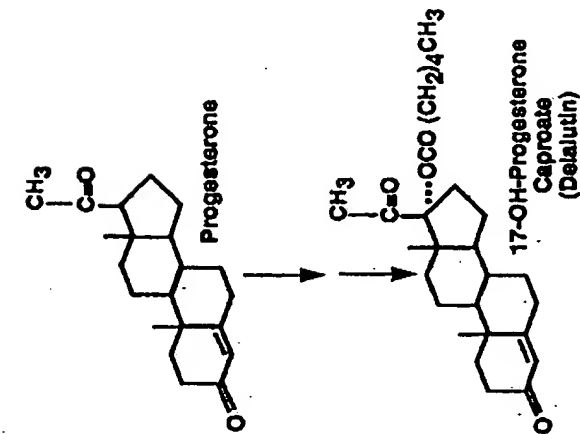
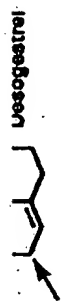


Figure 3. C-21 pregnane progestins.

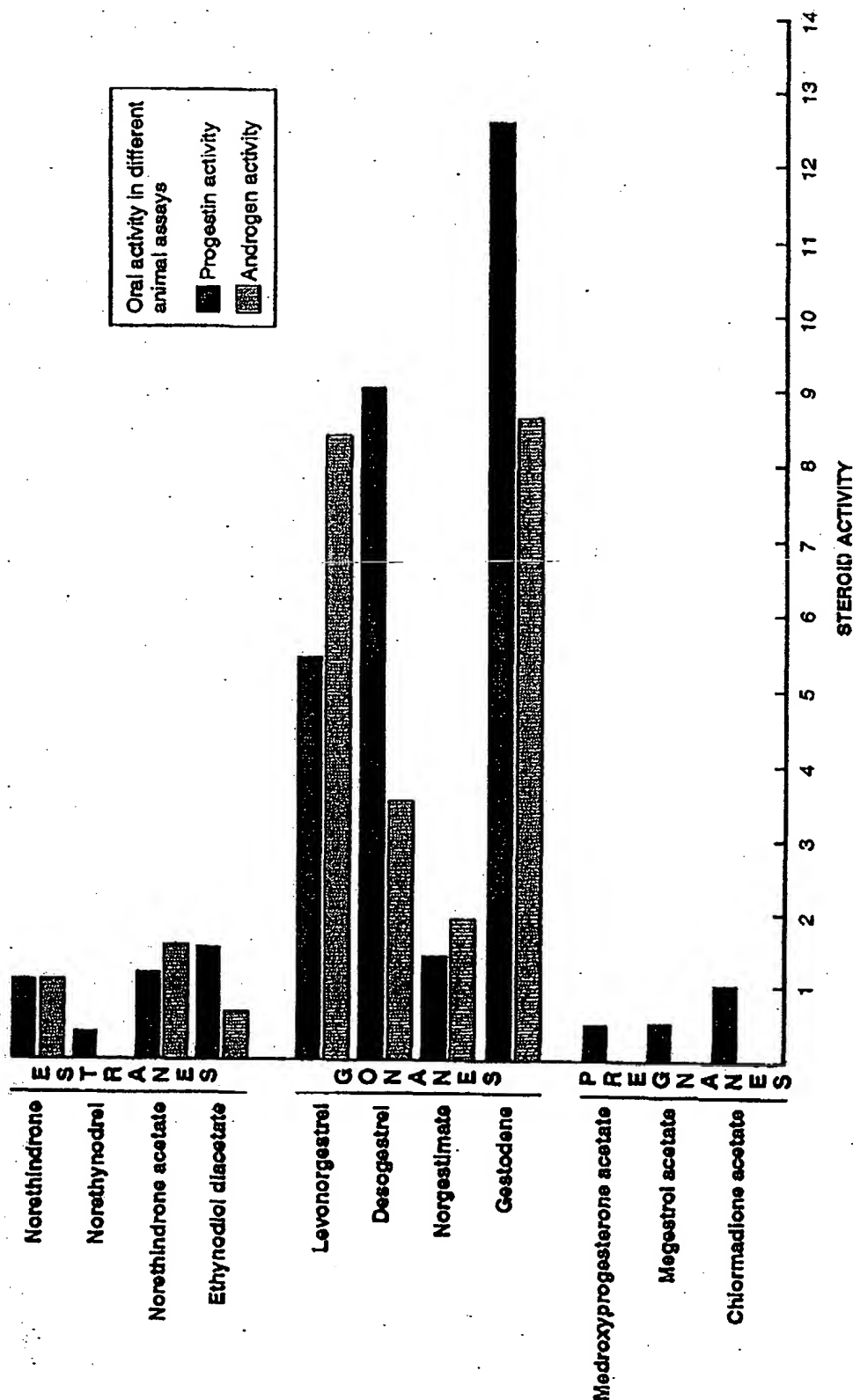


Figure 4. See legend on opposite page

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Each progestin has a different affinity for sex hormone-binding globulin (SHBG) and can modulate the levels of SHBG, as can the estrogens with which they are used. The relationship between estrogen and progestin interactions has variously been described as the simple algebraic sum of their biologic activity (biogebralic),<sup>36</sup> and as a complex interaction between the effects of the estrogen and progestin components. These effects can result in the displacement of different amounts of free testosterone from SHBG, producing variable degrees of androgenicity. Several studies have shown different affinities of the new progestins for SHBG relative to LNG.

The half-lives of progestins range from about 10 hours (oral medroxyprogesterone acetate, megestrol acetate, norethindrone, and desogestrel) to more than 2 days (LNG and norgestimate). Use of compounds with a longer half-life may permit the suppression of gonadotropins during the 7-day placebo phase of the pill<sup>30</sup> and, by corollary, may help alleviate hot flashes when used in sequential HRT. The intramuscular form of MPA, Depo-Provera, has an elimination half-life of about 50 days.

Estranes are converted to norethindrone, although not completely, and thus formulations that use these compounds may lower progestin potency and side effects.<sup>30</sup> Norethynodrel has been noted to have some estrogenic activity on endometrium. Although some investigators believe that this is the result of traces of mestranol left over from the synthetic process, other authors<sup>46</sup> have demonstrated that all the estranes have weak binding to the estrogen receptor protein. Norgestrel exists as a 50:50 racemic mixture, the D-form of which is biologically inactive. Its purified form is levonorgestrel; thus, at any dose, LNG has twice the potency of D/L-norgestrel.

The new gonane progestins, all derivatives of norgestrel, have been used in Europe for more than a decade and were recently introduced into the United States. Desogestrel is converted in two steps into its active metabolite 3-ketodesogestrel<sup>34</sup> (11-methylene LNG). Norgestimate is biologically active as are its metabolites 17-deacetylnorgestimate, D-norgestrel, levonorgestrel, and 3-ketonorgestimate.<sup>60</sup> Gestodene has the highest progestogenic activity of the newer compounds as well as a marked affinity for the aldosterone receptor protein.<sup>18</sup> Oral contraceptive formulations using desogestrel are now the most prescribed in Europe. To date, no United States formulation contains gestodene.

In 1988, following a published assertion<sup>47</sup> that ethinyl estradiol (EE) levels appeared elevated among women using gestodene-containing formulations, an apparent increase in thromboembolism was noted in anecdotal reports of complications to the German government. No increase in phlebitis, however, has been demonstrated clinically with the use of any OC containing the new progestins, gestodene and desogestrel.<sup>44</sup> No association with thrombophlebitis was found in controlled clinical trials with estrogen replacement therapy.<sup>5</sup>

Based on the compilation of data<sup>14, 18, 52, 67, 93</sup> by Dickey,<sup>13</sup> the activities of different oral progestins in animal assays with respect to progestagenic and androgenic effects are shown in Figure 4. In these pharmacologic studies, as well as in many others, gestodene is the most powerful progestin. Gonanes, other than norgestimate, have higher progestagenic activity than estranes in receptor-binding and bioassays (see Fig. 4). Unfortunately, the C18 methylation of the

**Figure 4.** Biologic activity of selected progestins. Oral activity in different animal assays: black bar = progestin activity, shaded bar = androgen activity. (Data from references 13, 14, 18, 52, 67, and 93.)

gonanes accorded increased progestogenic potency but also enhanced the androgenic activity of the molecule.<sup>52</sup> Norethynodrel, as well as the pregnanes, are without androgenic activity in the studies of Phillips,<sup>67</sup> on which Figure 4 is based; although Bergink<sup>3</sup> indicated that the pregnanes, particularly MPA, have small but measurable binding to androgen receptors.

Figure 5 represents progestagenic selectivity calculated from the same compilation of data used in Figure 4. Selectivity is the ratio between the desired and undesired pharmacologic effects, in this case the ratio of progesterone-mediated effects to those of androgen. In theory, this means that, at the therapeutic dose used, the drug has a far greater effect on the system intended to be manipulated than on other systems. Although, using these data, desogestrel is the most selective of the synthetic progestins studied and is marketed by its manufacturer as such, ethynodiol diacetate, the progestin in the OC Demulen is equally selective, although one tenth as potent by weight. Several in vitro receptor-binding preparations show similar trends. Other data from Phillips et al<sup>67</sup> suggested that norgestimate is the most specific of the three new progestins. Kloosterboer,<sup>52</sup> using a different progestin as the reference compound, showed gestodene to be the most selective. It should be cautioned, however, that these results are based on bioassays in different species and tissues (from rabbit endometrium to rat ventral prostate) and, in effect, are evaluating data from "apples and oranges." In addition, activities of the parent compounds, not their active metabolites, were used. Receptor-binding and bioassay data may not extrapolate to humans. Discrepancies may well exist among biochemical, animal, human biologic activity, and clinical spectrum. For example, if all estranes are metabolized to norethindrone, it would be anticipated that they would have identical profiles in vivo. Variables influencing biochemical assays include choice of tissue and species, intact versus fractionated cells, and other incubation conditions. Overall effect may vary by dose, formulation, and combination with estrogen. Currently, it is too early to evaluate whether enhanced selectivity will translate into decreased risk of serious sequelae. No study to date has shown any clinical significance of enhanced selectivity.

## CLINICAL EFFECTS

Although progestins are the primary active compound in OCs, estrogen being present for cycle control, progestins play a secondary but important role in HRT. They were added to prevent changes that had been noted with unopposed estrogen administration, allaying the major fear of endometrial carcinoma, which may prevent patients from using HRT.

Steroid hormones are known to affect a myriad of systems. This review concentrates on the benefits for which HRT is most commonly prescribed, endometrial protection, cardiovascular disease, osteoporosis, and vasomotor flushes, and briefly reviews one controversial area, the possible effect on carcinoma of the breast. A comprehensive literature review<sup>29</sup> regarding the risks and benefits and effect on life expectancy of HRT as well as clinical guidelines of the American College of Physicians<sup>30</sup> have recently been published.

### Effects on Endometrium

Retrospective studies<sup>80, 106</sup> published in 1975 showed an increase in endometrial hyperplasia and carcinoma in women treated with estrogen alone, which, in most patients, may be prevented by the addition of a progestational agent. The

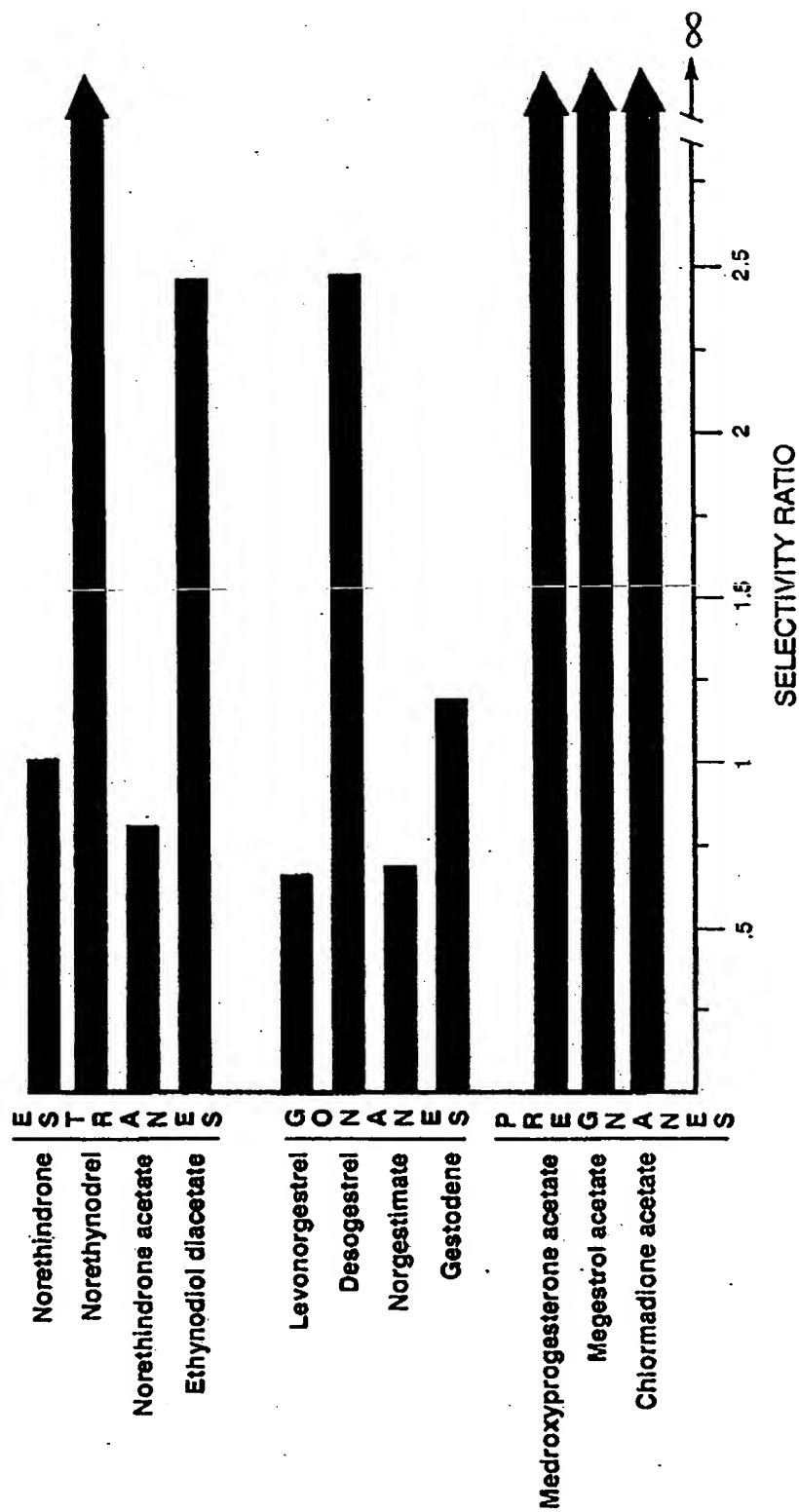


Figure 5. Selectivity of progestin. Ratio of progestin to androgen activity of oral steroids in animal assays. (Data from references 13, 14, 18, 52, 67, and 93.)

addition of progestin, as in combined estrogen-progestin therapy, can actually lower the incidence of the development of endometrial hyperplasia<sup>102</sup> and carcinoma.<sup>25</sup> In a 5-year prospective study with 4-year follow-up results, Gambrell et al<sup>25</sup> reported that the incidence of endometrial carcinoma was significantly decreased from 248 out of 100,000 women in the general population to 56 out of 100,000 women, figures that are lower than those in the control group without therapy, thereby making the use of HRT a form of prophylaxis compared with women who do not use HRT. Varma<sup>27</sup> reported that the addition of a progestin for more than 10 days monthly resulted in no evidence of cystic hyperplasia in 392 women. Other authors<sup>7, 25</sup> demonstrated that the addition of a progestin decreased the rate of hyperplasia from more than 20% without progestins to less than 1% if progestins were added for 12 or 13 days. Over time, doses of progestin used in HRT have been decreased without adverse effects on the endometrium. A limit to the beneficial effect has been demonstrated histologically and biochemically at higher doses of norethindrone and norgestrel,<sup>103</sup> possibly because of decreasing levels of estrogen-induced progesterone receptors or enzymes.

### Cardiovascular Disease, Lipids, and Lipoproteins

It is predicted that almost 60 million persons, 20% of the US population, will be more than 65 years old in the year 2025. Cardiovascular diseases account for the deaths of over half a million women annually in the United States; more than 50% of these deaths are the result of ischemic heart disease. Dozens of studies have demonstrated an apparent relationship between serum lipoproteins and heart disease. Many of these studies, however, have been performed only in men with the results extrapolated to women, which is unacceptable. Although not all authorities agree that the death rates from arterial disease increase after menopause, other than the increase from premature surgical oophorectomy,<sup>11</sup> a number of studies of different designs, including tens of thousands of women, have shown an apparent 50% to 70% decrease in the risk from coronary heart disease in women taking oral estrogen.<sup>2, 37, 84, 85, 86</sup>

The first observational reports of the benefit of estrogen replacement therapy appeared in two sequential articles in the October 1985 volume of the *New England Journal of Medicine*, presenting data from the Nurses' Health<sup>86</sup> and Framingham studies.<sup>104</sup> The latter study initially proposed an increased risk; however, reanalysis of the data showed a 50% protection against coronary artery disease, bringing the conclusions in line with many other studies published to date.<sup>16</sup> Similar results have been documented more recently with combined (estrogen and progesterone) HRT.<sup>22, 62, 94</sup> Several mechanisms have been postulated to mediate this beneficial impact. These include direct effects on endothelial elements in vessels; secretion of vasoactive peptides leading to vasodilation; a balance between thrombotic and atherogenic mechanisms<sup>71</sup>; and changes in carbohydrate, prostacyclin, or lipoprotein metabolism.<sup>29</sup> Lipid changes seen with HRT may be a benefit of pharmacologic doses rather than being a physiologic effect of "replacing" missing hormones.

The Lipid Research Clinic study<sup>6</sup> concluded that about 30% of cardiovascular risk is due to lipoproteins. Much of the data to date related to the effect of progestins on the cardiovascular system have investigated the impact of lipids and lipoprotein mechanisms.

Lipoproteins are high-molecular weight proteins that transport lipids through the plasma. The polar lipids form a core, predominantly triglycerides in very low-density lipoprotein (VLDL) and cholesterol ester in high-density lipo-

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protein (HDL) and low-density lipoprotein (LDL). This core is surrounded by a surface coat of hydrophilic phospholipids, including apoproteins (A-I and A-II in HDL and B-100 in LDL) that help to maintain particle solubility and to direct the lipoproteins to their site of metabolism by binding to cell membrane receptors. During the process that begins with intestinal chylomicron formation, proportionally more triglyceride is removed leaving a higher concentration of cholesterol. In order of increasing density, this leaves VLDL, LDL, and HDL, HDL<sub>2</sub>, HDL<sub>2a</sub>, and HDL<sub>2b</sub>. Normally as triglycerides are removed, remnants (intermediate-density lipoproteins [IDL]) and LDLs are returned to the liver and taken up by hepatic receptors. Multiple factors, including increased dietary fat, may result in excess levels of circulating remnants in the plasma. Oxidation of IDL and LDL is thought to result in the accumulation of lipids in arterial wall macrophages, initiating atherosclerosis. High-density lipoprotein is thought to play a role in "reverse cholesterol transport" of lipids from cells to the liver for excretion. High-density lipoprotein appears to provide a protective effect,<sup>28</sup> and LDL correlates with an increased risk of heart disease. Estrogens, in general, are thought to increase HDL, triglycerides, and apoprotein B and to lower LDL, partially by decreasing levels of the enzyme hepatic lipase. Walsh et al,<sup>98</sup> in a study using oral estrogens, reported a 15% increase in HDL, a 16% decrease in LDL, and no appreciable advantage of doubling doses except on triglycerides after 3 months. A dose of transdermal estrogen, 0.05 mg, was shown to have no appreciable effect on HDL at 6 weeks,<sup>98</sup> but a significant effect was noted at 24 weeks with the 0.1 mg transdermal patch.<sup>98</sup> Some studies<sup>39, 91, 95</sup> showed the most dramatic effect on women with elevated cholesterol levels or coronary artery disease. The Leisure World study<sup>37</sup> looked at the effect of estrogens on women with previous myocardial infarction or cerebrovascular accident and reported a 50% decrease in risk of dying from subsequent myocardial infarction or cerebrovascular accident. Sullivan<sup>91</sup> evaluated women angiographically and noted that women with the worst coronary artery disease had a better 10-year survival than those not taking estrogen.

Estrogens and progestins, however, sometimes have opposing effects. Early studies<sup>21, 39, 40, 64, 94</sup> suggested that some progestins, particularly the "older" 19-norprogestins, may detrimentally affect cardiovascular risk by lowering HDL and triglycerides and elevating LDL, thereby potentially reversing some of the beneficial effects of estrogen. These studies, however, were often of short duration, small sample size, and used high doses of progestin (10 mg MPA or norethindrone acetate [NETA]). For example, the often-quoted Hirvonen<sup>39</sup> paper had only six patients in each of three study arms. Comparisons of natural progesterone with synthetic progestagens in sequential regimens demonstrated decreased levels of HDL with the synthetic progestagens but no adverse influence of natural progesterone on the beneficial changes in lipids from estrogen,<sup>33, 43, 64</sup> except that HDL was decreased with the 300 mg dose of progesterone.<sup>21</sup> Part of the discrepancies may be caused by the different assays used to measure lipoprotein levels. Estimation of levels of lipoproteins can be influenced by the expertise of the laboratory staff and the biochemical and mathematic techniques employed. For example, the Friedewald<sup>29</sup> formula, which is often used to calculate LDL and VLDL from total cholesterol and HDL, may give different values than when these are estimated using centrifugal density gradients.

Some longer-term studies<sup>97</sup> have shown that these short-term effects on lipids may be reversed over time, possibly because of the induction of enzymes. Since the late 1980s, reports of combined HRT have shown decreases in LDL and total cholesterol levels with modest changes in HDL over 1- to 5-year periods. In some instances, the change in HDL parallels that in estrogen only or placebo controls, and both tend to return to baseline levels after 1 year.<sup>9, 12, 42, 43, 99</sup> With continuous therapy over 5 years using estradiol 2 mg, NETA 1 mg, or a placebo,



**Table 1. SUMMARY OF EFFECTS OF PROGESTINS ON LIPOPROTEINS USING COMBINED OR SEQUENTIAL HORMONE REPLACEMENT THERAPY FOR MORE THAN 6 MONTHS**

Agent	Dose (mg)	Sequential or Combined	HDL	LDL	TG	TC
Estrogen only			↑	NS/↓	↑	NS
Progestin						
NETA	0.25-1.0	Both	NS/↓	↓	NS	↓
TTS-NETA	0.25	Sequential	NS	↓	↓	↓
		Combined	NS	NS	NS	NS
D/L-NG	0.075-0.5	Sequential	NS/↓	↓	NS/↓	↓
	0.25	Combined	↓	↓	↓	↓
LNG	0.075	Sequential	NS	↓	—	—
MPA	10	Sequential	NS/↓	NS/↓	NS	↓
	5	Both	↑/NS	NS/↓	↑/NS	NS/↓
	2.5	Combined	↑/NS	NS/↓	NS	NS/↓
CPA	1.0	Sequential	NS	↓	NS	↓
Megace	7.5	Sequential	NS	↓	↓	↓
	5	Combined	NS	↓	NS	↓
	2.5	Combined	NS	NS	↑	NS
Micr Prog	200	Both	↑/NS	↓	NS	NS/↓
DSG	0.15	Sequential	↑/NS	↓	NS/↓	NS/↓
		Combined	↓	↓	↓	↓

CPA = cyproterone acetate; D/L-NG = D/L-norgestrel; DSG = desogestrel; HDL = high density lipoproteins; LDL = low density lipoproteins; LNG = levonorgestrel; Micr Prog = micronized progesterone; MPA = medroxyprogesterone acetate; NET = norethindrone; NETA = norethindrone acetate; NS = not significant; TC = total cholesterol; TG = triglycerides; TTS-NET = transdermal norethindrone; ↑ = significant increase; ↓ = significant decrease.

total cholesterol and LDL each were reduced 20% in the HRT group, triglycerides were unchanged, and HDL was reduced in both the treated and control groups.<sup>8</sup>

Table 1 is a summary of available data regarding the effect of combined\* and sequential† HRT for greater than 6 months on lipoprotein levels. Other than one report of opposing effects on triglycerides,<sup>12</sup> little difference is seen between oral or transdermal forms of progestin, using either low-dose 19-norprogestins or C-21 pregnane progestins, including MPA, megestrol and cyproterone acetate. Note that the 2.5 and 5 mg doses of MPA, 200 mg dose of micronized progesterone, and the 0.15 mg sequential dose of desogestrel have effects similar to those seen with unopposed estrogen. This may be the result of the lower doses used rather than the specific progestins. However, the decrease in HDL and triglycerides, as well as LDL and total cholesterol, with 0.15 mg of desogestrel in combined HRT<sup>27a</sup> does not support this theory. Cyclic variations continue to be seen in HDL and apo A-I levels between the estrogen only and estrogen-progesterone phases in combined-sequential HRT; these were exaggerated in smokers.<sup>32</sup>

Many researchers and clinicians believe that the new progestins may have important advantages over those now in use, such as fewer changes in lipid metabolism, thereby potentially diminishing the risk of cardiovascular problems. At the present time, no US studies have appeared, and few foreign studies use the new progestins in HRT. Published reports currently are limited to desogestrel. Foreign studies, in general, have few controls and compare fixed HRT combinations in which both estrogens and progestins differ between study arms.

\*References 8, 9, 33, 42, 57, 57a, 59, 70, 83, 99, 105, 107.

†References 2, 21, 33, 39, 41, 43, 55, 57, 58, 66, 69, 70, 74, 78, 92, 105.

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The majority used sequential regimens of estrogen and MPA 5 mg, NETA 1 mg, LNG 75 µg, or desogestrel 150 µg for 10 days per month and reported significant decreases in LDL and minor or cyclic changes in HDL.<sup>31, 58</sup> Only a report from Israel<sup>72</sup> showed an advantage with the new progestin, desogestrel, compared with sequential doses of MPA and NETA. Over a 9-month period, HDL was calculated to increase 30% with desogestrel, 20% with MPA, and not significantly with NETA. However, NETA was used at a 1-mg dose in combination with estradiol and estriol, whereas conjugated equine estrogens were matched with different durations of desogestrel and MPA use. Low-density lipoprotein decreases were 10% (MPA), 15% (NETA), and 27% (desogestrel). To date, no direct comparison has been made of the effectiveness of the three new progestins other than in OCs in which desogestrel, norgestimate, and gestodene appear to increase triglyceride levels and have no significant effect on LDL or total cholesterol.<sup>73</sup> A recent review<sup>48</sup> shows desogestrel having different effects on lipoproteins when used in OCs increasing HDL and triglycerides and having no significant change in LDL level; one might speculate that these differences are caused by the greater proportion of estrogen in OCs.

Many studies, particularly with continuous HRT, show a decrease in LDL and total cholesterol over time. Three studies,<sup>32, 59, 83</sup> however, demonstrated no significant change in HDL/LDL or total cholesterol/LDL ratios with combined-continuous HRT. Even if both HDL and LDL are reduced, a beneficial effect may occur when the reduction of LDL is greater than that of HDL. Conversely, if studies show the beneficial effect persists in the presence of lipoprotein levels returning to baseline levels, this may imply indirect support of some of the other hypotheses mentioned previously. In addition, it is not yet known whether a statistically significant change in levels will also be clinically significant. A recent observational study has documented that HRT is associated with such a favorable physiologic profile,<sup>62</sup> but further randomized trials are required. The ongoing Women's Health Initiative<sup>11a</sup> may help to answer this question.

### Osteoporosis

Osteoporosis affects 15 to 20 million women—half to one third of postmenopausal women. It is estimated to result in 1.3 million fractures annually and to cost 7 to 10 billion dollars a year in the United States. Peak cortical bone density occurs in women at 35 years of age, whereas trabecular density occurs somewhat earlier and decreases rapidly 3 to 7 years after menopause, about 15% every 10 years. Bone mass is affected by a number of additional variables, including age, genetics, calcium, medications, activity, smoking, and coexisting medical conditions.

Absorption of calcium in the gastrointestinal tract appears to be compromised in menopausal women and improved by estrogen replacement. An increase in oral calcium intake, however, is not enough.<sup>72</sup> Estrogen has been documented to increase absorption of calcium in the gastrointestinal tract, decrease bone resorption, and retard postmenopausal bone loss.<sup>27, 36</sup> Estrogen may prevent up to 80% of vertebral compression fractures and 50% to 60% of fractures of the hip and arm. No data are available relating to the effect of estrogen on death rate from hip fracture. A recent report,<sup>2a</sup> however, indicated that at least 7 years of estrogen therapy after menopause are needed for long-term protection of bone mineral density, and even this may not protect women aged 75 years and older.

There is evidence<sup>9, 69</sup> that combined estrogen and progestin therapy prevents postmenopausal bone loss, possibly uncoupling of bone formation and resorp-

tion.<sup>10</sup> Others<sup>19, 43, 57, 58, 76, 89</sup> have shown that various combinations of estrogen and progestins, including the transdermal form of progestins, may lead to increased bone formation. Lee<sup>53</sup> hypothesized that progesterone, not estrogen, is the missing factor in the prevention and treatment of osteoporosis. A few studies<sup>35, 58, 74</sup> (although again of questionable, suboptimal design) that compared desogestrel with the older progestins demonstrated reversal of indexes of bone resorption, decreased bone turnover, and prevention of bone loss. More work is needed to clarify the relationship between the effect of estrogen and progesterone and whether any benefit will be derived from use of the new progestins.

### Vasomotor Flashes

Vasomotor flashes ("hot flashes") occur in 85% to 90% of menopausal and postmenopausal women and are the reason many women seek medical assistance during the climacteric. Estrogen has been shown to decrease or eliminate hot flashes. In a randomized, double-blind crossover study, Campbell and Whitehead<sup>7</sup> using estrogen 1.25 mg, showed that hot flashes were substantially reduced and sleep was increased. Schiff et al,<sup>75</sup> using a sleep unit, noted a decrease in sleep latency and an increase in REM sleep during estrogen therapy. Progesterone, however, has also been shown to alleviate vasomotor flashes. In women in whom estrogen but not progestin therapy is contraindicated, two progestins have been found to be efficacious in decreasing or relieving hot flashes: MPA, 10 to 40 mg/day or Depo-Provera, in 1- to 3-month intervals as needed; and megestrol acetate (Megace), 20 to 80 mg/day. Unfortunately, progestins do not provide the beneficial effects of estrogen on genital tissues, and some women experience vaginal dryness and resultant dyspareunia with these medications. No work to date has been published regarding the new progestins and vasomotor flashes. Other, nonsteroidal, methods for relief of flashes have been reviewed by Miller.<sup>61</sup>

### Carcinoma of the Breast and Hormone Replacement Therapy

Many women fear carcinoma of the breast far more than heart disease or osteoporosis, although the risk of death from cardiovascular disease is about 10 times greater. Some women decline the use of HRT and hormonal contraception despite the lack of current data clearly demonstrating that estrogens or progestins affect the risk of developing breast carcinoma, a risk that increases linearly with age in all women. A variety of studies have been performed to try to elucidate the relationship between sex steroids and carcinoma of the breast. For many years, it was assumed that the breast, like the endometrium, would respond to progesterone stimulation with a protective effect. But biochemical differences in response to progesterone stimulation have been demonstrated<sup>102</sup> between these two tissues. To date, more than 40 studies in the English literature have investigated the question of HRT with and without progestins and breast carcinoma without a clear consensus. Data from Gambrell et al<sup>24</sup> appear to document a protective effect of progesterone with respect to cancer. Two Scandinavian reports<sup>4, 20</sup> suggest the converse. Several large studies show no increased risk. Therefore, until such a positive relationship is more clearly documented, many authorities<sup>39, 100</sup> recommend using estrogen-only HRT in women who have undergone hysterectomy in view of the potential detrimental effects of progestins on cardiovascular risk.

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## DOSE RECOMMENDATIONS

Hormone replacement therapy currently is prescribed both sequentially and continuously. The classic sequential method attempts to simulate the hormone pattern of premenopausal women and produces a secretory endometrium. Most regimens combine 10 to 14 days of a progestin with 25 days of estrogen per month, although no additional risk of endometrial hyperplasia was demonstrated by combining daily estrogen with cyclic MPA.<sup>33</sup> Using endometrial biopsies, Padwick and colleagues<sup>65</sup> documented that a 5-mg dose of progesterone may be used safely. Women who bleed before day 10 of progestin administration often require a higher dose in subsequent cycles to produce full conversion to a secretory endometrium.<sup>65</sup> Unfortunately, a large number of women experience withdrawal bleeding well into their 60s with the sequential combination.

Recently, the so-called continuous-combined method that involves a constant daily dose of both estrogen and progestin has come into vogue. Its primary advantages include the use of a lower daily dose of progestin, which potentially results in fewer adverse metabolic changes and side effects; these include the dysphoric effects on mood<sup>77</sup> noted with some preparations, as well as breast tenderness, bloating, and headache. In addition, these regimens eventually produce amenorrhea from an atrophic endometrium. On the negative side, however, up to 80% of women experience breakthrough bleeding in the first 6 months and 10% at 12 months. The bleeding in both this and the classic sequential HRT method often results in a major problem with compliance.

Standard estrogen doses, with both sequential and combined regimens, include conjugated (0.625 mg), micronized (1 to 2 mg), or transdermal (0.05 mg) estrogen. In many instances, current doses of progestin in HRT are similar to those in OC preparations. Although equivalent potencies of oral progestins on estrogen-primed endometrium were shown by King and Whitehead<sup>50</sup> to be 5 mg of medroxyprogesterone, 0.35 mg norethindrone, 0.075 mg of D/L-norgestrel, and 200 mg micronized progesterone, the standard dosages of progestins in the sequential regimens usually are 5 to 10 mg of medroxyprogesterone acetate (Provera, Cycrin, Amen), 0.075 mg D/L-norgestrel (Ovrette), 2.5 to 5 mg norethindrone (Micronor, Norlutin, NorQD), 5 to 10 mg norethindrone acetate (Norlutate, Aygestin), 150 µg desogestrel, or 200 mg of micronized oral progesterone daily for 10 to 14 days. Daily continuous combinations usually involve MPA 2.5 to 5 mg, norethindrone 0.35 to 2.1 mg, norethindrone acetate 1 mg, or desogestrel 150 µg/day. Alternate treatments include 250 µg/day of levonorgestrel (Norplant) or Depo-Provera every second or third month to decrease withdrawal bleeding. The longer-term effects on endometrium with these regimens are not yet clear. All of the new progestins are dosed lower than most other commonly used progestins. As mentioned previously, desogestrel has been used at 150 µg daily in both continuous and sequential regimens. Norgestimate has been used effectively in European OCs at daily doses as low as 250 µg and gestodene at 75 µg. Studies being conducted with considerably lower doses may show them to be equally efficacious in HRT with lowered effects on lipids. When it is necessary to use unopposed estrogen, endometrial sampling has been recommended annually or when the endometrial stripe becomes greater than 4 to 8 mm on transvaginal ultrasonography.<sup>54</sup> Archer et al<sup>1</sup> have reported that pretreatment biopsy is unjustified in asymptomatic women with a less than 0.75% yield of cancer or atypia.

## ON THE HORIZON

To improve convenience and compliance, many parenteral combinations of steroids have been postulated, some of which are being tested. These include

injectable suspensions and microspheres, transdermal patches combining estrogen and progestagens,<sup>49, 55, 56, 102</sup> subdermal implants, such as the Norplant system, and some biodegradable varieties of implants and pellets. Vaginal rings, when investigated for contraceptive use, produced satisfactory blood levels of hormones.<sup>51</sup> Use of progesterone intrauterine devices, which release 65 mg progesterone daily,<sup>79</sup> have been described for the prevention of endometrial hyperplasia in postmenopausal women.

## CONCLUSION

The first hormonal contraceptive combination, introduced in 1960, contained mestranol 150 µg, and norethynodrel 10 mg. Both contraceptive and hormone replacement doses have dropped more than 90% in the intervening years. The current ratio of progestin to estrogen dose in OCs by weight covers a range of more than tenfold, from less than 5 to 50. The biologic activity of the estrogens in OCs, now predominantly ethenyl estradiol, has been shown to be many times that of the estrogens used in HRT. Accordingly, the potential exists for progestin doses in HRT to be decreased even further in the future with the possibility of additional reduction in adverse effects. It is too early to see whether the new progestins will offer any clinical advantages over older compounds. Current data do not uniformly support this concept. Conversely, an optimal combination of estrogen and progestins for prevention of osteoporosis has not yet been determined, nor has a consensus been reached about the effect of steroid hormones on carcinoma of the breast. Therefore, the optimal regimen and route of HRT await the results of future studies.

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## References

1. Archer DF, McIntyre-Saltman K, Wilborn WW Jr, et al: Endometrial morphology in asymptomatic postmenopausal women. *Am J Obstet Gynecol* 165:317-322, 1991
2. Barrett-Connor E, Bush TL: Estrogen replacement and coronary heart disease. *Cardiovascular Clinics* 19:159-172, 1989
3. Bergink EW, van Meel F, Turpijn EW, et al: Binding of progestagens to receptor proteins in MCF-7 cells. *J Steroid Biochem Mol Biol* 19:1563-1570, 1983
4. Bergkvist L, Adami HO, Persson I, et al: The risk of breast cancer after estrogen and estrogen-progestin replacement. *N Engl J Med* 321:293-297, 1989
5. Boston Collaborative Drug Surveillance Program: Surgically confirmed gallbladder disease, venous thrombosis, and breast tumors in relation to postmenopausal estrogen therapy. *N Engl J Med* 290:15-19, 1974
6. Bush TL, Barratt-Connor E, Cowan LD, et al: Cardiovascular mortality and noncontraceptive use of estrogen in women: Results from the Lipid Research Clinic's program follow-up study. *Circulation* 75:1102-1109, 1987
7. Campbell S, Whitehead M: Oestrogen therapy and the menopausal syndrome. *Clin Obstet Gynecol* 4:31-47, 1977
8. Cano A, Fernandes H, Serrano S, et al: Effect of continuous oestradiol-medroxyprogesterone administration on plasma lipids and lipoproteins. *Maturitas* 13:35-42, 1991

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9. Christiansen C, Riis BJ: Five years with continuous combined oestrogen/progestogen therapy: Effects on calcium metabolism, lipoproteins, and bleeding pattern. *Br J Obstet Gynaecol* 97:1087-1092, 1990
10. Christiansen C, Riis BJ, Nilas L, et al: Uncoupling of bone formation and resorption by combined oestrogen and progestagen therapy in postmenopausal osteoporosis. *Lancet* 2:800-801, 1985
11. Colditz GA, Willett WC, Stampfer MJ, et al: Menopause and the risk of coronary heart disease in women. *N Engl J Med* 316:1105-1110, 1987
- 11a. Cotton P: Women's health initiative leads way as research begins to fill gender gaps. *JAMA* 267:469-470, 473, 1992
12. Crook D, Cust MP, Gangar KF, et al: Comparison of transdermal and oral estrogen-progestin replacement therapy: Effects on serum lipids and lipoproteins. *Am J Obstet Gynecol* 166:950-955, 1992
13. Dickey RP: *Managing Contraceptive Pill Patients*, ed 7. Durant, OK, Essential Medical Information Systems Inc, 1993
14. Dickey RP, Stone SC: Progestational potency of oral contraceptives. *Obstet Gynecol* 47:106-112, 1976
15. Djerassi C, Miramotes L, Rosenkianz G: [abstracts]. American Chemical Society, April 1951, p 18
16. Eaker ED, Castelli WP: Coronary heart disease and its risk factors among women in the Framingham study. In Eaker ED, Packard B, Wenger NK, et al (eds): *Coronary Heart Disease in Women*. Proceedings of an NIH workshop. New York, Haymarket Doyma Inc, 1987, pp 122-130
17. Edgren RA: Oral contraception: A review. *Int J Fertil* 36(Suppl 3):16-25, 1991
18. Elger W, Steinbeck H, Schillinger E, et al: Endocrine-pharmacological profile of gestodene. *Advances in Contraceptive Delivery Systems* 2:182-197, 1986
19. el-Hajj Fuleihan G, Brown EM, Curtis K, et al: Effects of sequential and daily continuous hormone replacement therapy on indexes of mineral metabolism. *Arch Intern Med* 152:1904-1909, 1992
20. Ewertz M: Influence of noncontraceptive exogenous and endogenous sex hormones on breast cancer risk in Denmark. *Int J Cancer* 42:832-838, 1988
21. Fåhræus L, Larsson-Cohn U, Wallentin L: L-norgestrel and progesterone have different influences on plasma lipoproteins. *Eur J Clin Invest* 13:447-453, 1983
22. Falkeborn M, Persson I, Adami H-O, et al: The risk of acute myocardial infarction after oestrogen and oestrogen-progestogen replacement. *Br J Obstet Gynaecol* 99:821-828, 1992
- 22a. Felson DT, Zhang Y, Hannan MT, et al: The effect of postmenopausal estrogen therapy on bone density in elderly women. *N Engl J Med* 329:1141-1146, 1993
23. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma without the use of preparative ultracentrifugation. *Clin Chem* 18:499-502, 1972
24. Gambrell RD Jr, Maier RC, Sanders BI: Decreased incidence of breast cancer in postmenopausal estrogen-progestogen users. *Obstet Gynecol* 62:435-443, 1983
25. Gambrell RD Jr, Massey FM, Castaneda TA, et al: Use of the progestogen challenge test to reduce the risk of endometrial cancer. *Obstet Gynecol* 55:732-738, 1980
26. Goldzieher JW: Thirty years of hormonal contraception: A historical perspective. *Int J Fertil* 36(Suppl 3):10-15, 1991
27. Gordan GS, Vaughan C: NIH Consensus Conference: Osteoporosis: Calcium and osteoporosis. *J Nutr* 116:319-322, 1986
28. Gordon T, Castell WP, Hjortland MC, et al: High density lipoprotein as a protective factor against coronary heart disease: The Framingham study. *Am J Med* 62:707-714, 1977
29. Grady D, Rubin SM, Petitti DB, et al: Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 117:1016-1040, 1992
30. Guidelines for counseling postmenopausal women about preventative hormone therapy. *Ann Intern Med* 117:1038-1041, 1992
31. Haarbo J, Christiansen C: Treatment-induced cyclic variations in serum lipids, lipoproteins, and apolipoproteins after 2 years of combined hormone replacement therapy: Exaggerated cyclic variations in smokers. *Obstet Gynecol* 80:639-644, 1992

32. Haarbo J, Hassager C, Jensen SB, et al: Serum lipids, lipoproteins, and apolipoproteins during postmenopausal estrogen replacement therapy combined with either 19-nortestosterone derivatives or 17-hydroxyprogesterone derivatives. *Am J Med* 90:584-589, 1991
33. Hargrove JT, Maxson WS, Wentz AC, et al: Menopausal hormone replacement therapy with continuous daily oral micronized estradiol and progesterone. *Obstet Gynecol* 73:606-612, 1988
34. Hasenack HG, Bosch AMG, Käär K: Serum levels of 3-keto-desogestrel after oral administration of desogestrel and 3-keto-desogestrel. *Contraception* 33:591-596, 1986
35. Hassenger C, Colwell A, Assiri AMA, et al: Effect of menopause and hormone replacement therapy on urinary excretion of pyridium cross-links: A longitudinal and cross-sectional study. *Clin Endocrinol* 37:45-50, 1992
36. Heany P, Recker RR, Saville PD: Menopausal changes in calcium balance performance. *J Lab Clin Med* 92:953-963, 1978
37. Henderson BE, Paganini-Hill A, Ross RK: Estrogen replacement therapy and protection from acute myocardial infarction. *Am J Obstet Gynecol* 159:312-317, 1988
38. Henderson BE, Pike MC, Ross RK, et al: Reevaluating the role of progestogen therapy after the menopause. *Fertil Steril* 49:9S-15S, 1988
39. Hirvonen E, Mäkönen M, Manninen V: Effects of different progestogens on lipoproteins during postmenopausal replacement therapy. *N Engl J Med* 304:560-563, 1981
40. Jensen J, Nilas L, Christiansen C: Cyclic changes in serum cholesterol and lipoproteins following different doses of combined post-menopausal hormone replacement therapy. *Br J Obstet Gynaecol* 93:613-618, 1986
41. Jensen J, Riis BJ, Christiansen C: Cyproterone acetate: An alternative progestogen in postmenopausal hormone replacement therapy? Effects on serum lipids and lipoproteins. *Br J Obstet Gynaecol* 94:136-137, 1987
42. Jensen J, Riis BJ, Ström V, et al: Continuous oestrogen-progestogen treatment and serum lipoproteins in postmenopausal women. *Br J Obstet Gynaecol* 94:130-135, 1987
43. Jensen J, Riis BJ, Ström V, et al: Long-term effects of percutaneous estrogens and oral progesterone on serum lipoproteins in postmenopausal women. *Am J Obstet Gynecol* 156:66-71, 1987
44. Jespersen J, Peterson KR, Skouby SV: Effects of newer oral contraceptives on the inhibition of coagulation and fibrinolysis in relation to dosage and type of steroid. *Am J Obstet Gynecol* 163:396-403, 1990
45. Jones KP: Estrogens and progestins: What to use and how to use it. In Pitkin RM, Scott JR (eds): *Estrogen Replacement Therapy*. Philadelphia, JB Lippincott Co, 1992, pp 871-883
46. Jones RC, Edgren RA: The effects of various steroids on the vaginal histology in the rat. *Fertil Steril* 24:284-291, 1973
47. Jung-Hoffman C, Kuhl H: Interaction with the pharmacokinetics of EE and progestogens contained in oral contraceptives. *Contraception* 40:299-312, 1989
48. Kafrissen ME, Corson SL: Comparative review of third-generation progestins. *Int J Fertil* 38(Suppl 3):103-113, 1993
49. Keller PJ, Hotz E, Inthurn B: A transdermal regimen for continuous combined hormone replacement therapy in menopause. *Maturitas* 15:195-198, 1992
50. King RJB, Whitehead M: Assessment of the potency of orally administered progestins in women. *Fertil Steril* 46:1062-1066, 1986
51. Kloosterboer HJ, Deckers GHJ: Desogestrel: A selective progestogen. *International Proceedings Journal* 1:26-30, 1989
52. Kloosterboer HJ, Vonk-Noordegraaf CA, Turpijn EW: Selectivity in progestin and androgen receptor binding of progestagens used in oral contraceptives. *Contraception* 38:325-332, 1988
53. Lee JR: Is natural progesterone the missing link in osteoporosis prevention and treatment? *Med Hypotheses* 35:316-318, 1991
54. Lin MC, Gosink BB, Wolf SI, et al: Endometrial thickness after menopause: Effect of hormone replacement. *Radiology* 180:27-32, 1991
55. Lindgren R, Berg G, Hammar M, et al: Plasma lipid and lipoprotein effects of transdermal administration of estradiol and estradiol/norethisterone acetate. *Eur J Obstet Gynecol Reprod Biol* 47:213-221, 1992

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l  
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74. S  
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b  
75. S  
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56. Lindgren R, Risberg B, Hammar M, et al: Endometrial effects of transdermal estrogen/norethisterone acetate. *Maturitas* 15:71-78, 1992
57. Luciano AA, De Souza MJ, Roy MD, et al: Evaluation of low-dose estrogen and progestin therapy in postmenopausal women: A double-blind, prospective study of sequential versus continuous therapy. *J Reprod Med* 38:207-214, 1993
- 57a. Marsh MS, Crook D, Whitcroft SL, et al: Effect of continuous combined estrogen and desogestrel hormone replacement therapy on serum lipids and lipoproteins. *Obstet Gynecol* 83:19-23, 1994
58. Marslew U, Riis BJ, Christiansen C: Desogestrel in hormone replacement therapy: Long-term effects on bone, calcium and lipid metabolism, climacteric symptoms, and bleeding. *Eur J Clin Invest* 21:601-607, 1991
59. Mattsson L-Å, Cullberg G, Samsioe G: A continuous estrogen-progestogen regimen for climacteric complaints: Effect on lipid and lipoprotein metabolism. *Acta Obstet Gynecol Scand* 63:673-677, 1984
60. McGuire JL, Phillips A, Hahn DW, et al: Pharmacologic and pharmacokinetic characteristics of norgestimate and its metabolites. *Am J Obstet Gynecol* 163:2127-2131, 1990
61. Miller KL: Alternatives to estrogen for menopausal symptoms. In Pitkin RM, Scott JR (eds): *Estrogen Replacement Therapy*. Philadelphia, JB Lippincott Co, 1992, p 884-893
62. Nabulsi AA, Folsom AR, White A, et al: Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. *N Engl J Med* 328:1069-1075, 1993
63. Orme ML'E, Back DJ: Factors affecting the enterohepatic circulation of oral contraceptive steroids. *Am J Obstet Gynecol* 163:2146-2151, 1990
64. Ottosson UB, Johansson BG, von Schoultz B: Subfractions of high-density lipoprotein cholesterol during estrogen replacement therapy: A comparison between progestogens and natural progesterone. *Am J Obstet Gynecol* 151:746-750, 1985
65. Padwick ML, Pryse-Davies J, Whitehead MI: A simple method for determining the optimal dosage of progestin in postmenopausal women receiving estrogens. *N Engl J Med* 315:930-934, 1986
66. Pang SG, Lozano K, Greendale GA, et al: Long-term effects of transdermal estradiol with and without medroxyprogesterone acetate. *Fertil Steril* 59:76-82, 1993
67. Phillips A, Demarest K, Hahn DW, et al: Progestational and androgenic receptor binding affinities and in vivo activities of norgestimate and other progestins. *Contraception* 41:399-410, 1990
68. Phillips A, Hahn DW, Klimmek S, et al: A comparison of potencies and activities of progestagens used in contraceptives. *Contraception* 36:181-192, 1987
69. Plunkett ER, Wolfe BM: Prolonged effects of a novel, low-dosage continuous progestin-cyclic estrogen replacement program in postmenopausal women. *Am J Obstet Gynecol* 166:117-121, 1992
70. Prough SG, Aksel S, Wiebe RH, et al: Continuous estrogen/progestin therapy in menopause. *Am J Obstet Gynecol* 157:1449-1453, 1987
71. Psaty BM, Heckbert SR, Atkins D, et al: A review of the association of estrogens and progestins with cardiovascular disease in postmenopausal women. *Arch Intern Med* 153:1421-1427, 1993
72. Riis B, Thomsen K, Christiansen C: Does calcium supplementation prevent postmenopausal bone loss? A double-blind controlled clinical study. *N Engl J Med* 316:173-177, 1987
- 72a. Roy S, Krauss RM, Mishell DR: The effects of lipids and lipoproteins of a contraceptive vaginal ring containing levonorgestrel and estradiol. *Contraception* 24:429-449, 1981
73. Runnebaum B, Rabe T: New progestogens in oral contraceptives, pt 4. *Am J Obstet Gynecol* 157:1059-1063, 1987
74. Saure A, Hirvonen E, Viinikka L, et al: The effect of a novel estradiol-desogestrel treatment on the bone in climacteric women. In Christiansen C, Overgaard K (eds): *Osteoporosis 1990. Third International Symposium on Osteoporosis, Denmark, October 14-18, 1990*, p 116
75. Schiff I, Regestein Q, Tulchinsky D, et al: Effects of estrogens on sleep and psychological state of hypogonadal women. *JAMA* 242:2405-2407, 1979



76. Selby PL, Peacock M, Barkworth SA, et al: Early effects of ethinyl oestradiol and norethisterone treatment in postmenopausal women on bone resorption and calcium regulating hormones. *Clin Sci* 69:265-271, 1985
77. Sherwin BB: The impact of different doses of estrogen and progestin on mood and sexual behavior in postmenopausal women. *J Clin Endocrinol Metab* 72:336-343, 1991
78. Sherwin BB, Gelfand MM: A prospective one-year study of estrogen and progestin in postmenopausal women: Effects on clinical symptoms and lipoprotein lipids, pt 1. *Obstet Gynecol* 73:759-766, 1989
79. Shoupe D, Meme D, Mezrow G, et al: Prevention of endometrial hyperplasia in postmenopausal women with intrauterine progesterone [letter]. *N Engl J Med* 325:1811-1812, 1991
80. Smith DC, Prentice R, Thompson DJ, et al: Association of exogenous estrogens and endometrial carcinoma. *N Engl J Med* 293:1164-1167, 1975
81. Smith H, Hughes EA, Douglas EH, et al: Totally synthetic (+ -) -13-alkyl-3-hydroxy- and methoxy-gona-1,3,5 (10)-tran-17-ones and related compounds. *Experientia* 19:394-376, 1963
82. Speroff L, Glass RH, Kase N: *Clinical Gynecologic Endocrinology and Infertility*, ed 4. Baltimore, Williams & Wilkins, 1989
83. Sporrang T, Hellgren M, Samsioe G, et al: Metabolic effects of continuous estradiol-progestin therapy in postmenopausal women. *Obstet Gynecol* 73:754-758, 1989
84. Stampfer MJ, Colditz GA: Estrogen replacement therapy and coronary heart disease: A quantitative assessment of the epidemiologic evidence. *Prev Med* 20:47-63, 1991
85. Stampfer MJ, Colditz GA, Willett WC, et al: Postmenopausal estrogen therapy and cardiovascular disease: Ten-year follow-up from the Nurses' Health Study. *N Engl J Med* 325:756-762, 1991
86. Stampfer MJ, Willett WC, Colditz GA, et al: A prospective study of postmenopausal estrogen therapy and coronary heart disease. *N Engl J Med* 313:1044-1049, 1985
87. Stanczyk FZ, Roy S: Metabolism of levonorgestrel, norethindrone and structurally related compounds. *Contraception* 42:67-96, 1990
88. Stanczyk FZ, Shoupe D, Nunez V, et al: A randomized comparison of nonoral estradiol delivery in postmenopausal women. *Am J Obstet Gynecol* 159:1540-1546, 1988
89. Stevenson JC, Cust MP, Gangar KF, et al: Effects of transdermal versus oral hormone replacement therapy on bone density in spine and proximal femur in postmenopausal women. *Lancet* 336:265-269, 1990
90. Stewart DL: The new oral contraceptives: Understanding the pharmacology. *The Female Patient* 18:69-71, 1993
91. Sullivan JM, Zwagg RV, Hughes JP, et al: Estrogen replacement and coronary artery disease: Effect on survival in postmenopausal women. *Arch Intern Med* 150:2557-2562, 1990
92. Tadmor OP, Kleinman Y, Goldstein R, et al: The effect of desogestrel for hormone replacement therapy on the blood lipid profiles of postmenopausal women. *Int J Gynecol Obstet* 39:105-110, 1992
93. Tausk M, de Visser J: *International Encyclopedia of Pharmacology and Therapeutics*, Ch 28, Sect 48, Vol 2. Elmsford, NY, Pergamon Press, 1972
94. Thompson SG, Meade TW, Greenberg G: The use of hormonal replacement therapy and the risk of stroke and myocardial infarction in women. *J Epidemiol Community Health* 43:173-178, 1989
95. Tikkanen MJ, Nikkilä EA, Kuusi T, et al: High density lipoprotein-2 and hepatic lipase: Reciprocal changes produced by estrogen and norgestrel. *J Clin Endocrinol Metab* 54:1113-1117, 1982
96. Upton GV: Lipids, cardiovascular disease, and oral contraceptives: A practical perspective. *Fertil Steril* 53:1-12, 1990
97. Varma TR: Effect of long-term therapy with estrogen and progesterone on the endometrium of postmenopausal women. *Acta Obstet Gynecol Scand* 64:41-46, 1985
98. Walsh BW, Schiff I, Rosner B, et al: Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N Engl J Med* 325:1196-1204, 1991
99. Weinstein L, Bewtra C, Gallagher JC: Evaluation of a continuous combined low-dose regimen of estrogen-progestin for treatment of the menopausal patient. *Am J Obstet Gynecol* 162:1534-1542, 1990

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100. Whitehead MI, Fraser D: Controversion concerning the safety of estrogen replacement therapy. *Am J Obstet Gynecol* 156:1313-1322, 1987
101. Whitehead MI, Fraser D, Schenkel L, et al: Transdermal administration of oestrogen/progestagen hormone replacement therapy. *Lancet* 335:310-312, 1990
102. Whitehead MI, King RJB, McQueen J, et al: Endometrial histology and biochemistry in climacteric women during oestrogen and oestrogen/progestin therapy. *J R Soc Med* 72:322-327, 1979
103. Whitehead MI, Townsend PT, Pryse-Davies J, et al: Effects of estrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium. *N Engl J Med* 305:1599-1605, 1981
104. Wilson PWF, Garrison RJ, Castelli WP: Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50: The Framingham Study. *N Engl J Med* 313:1038-1043, 1985
105. Yancey MK, Storie IK, Hannan CJ Jr, et al: Serum lipids and lipoproteins in continuous or cyclic medroxyprogesterone acetate treatment in postmenopausal women treated with conjugated estrogens. *Fertil Steril* 54:778-782, 1990
106. Ziel HK, Finkle WD: Increased risk of endometrial carcinoma among users of conjugated estrogens. *N Engl J Med* 293:1167-1170, 1975

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# **Treatment of the Postmenopausal Woman**

Basic and Clinical Aspects

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## CHAPTER 9

# Hot Flashes

Fredi Kronenberg

Hot flashes are the classic sign of menopause as well as the predominant complaint of perimenopausal and menopausal women in the United States, yet it was not until 1975 that serious scientific study of hot flashes was undertaken. In that year, a paper on the measurement of physiological changes during hot flashes demonstrated their objective existence (1), and the phenomenon could no longer be dismissed as being "all in the head," as it often had been previously.

A hot flash is a sudden, transient sensation ranging from warmth to intense heat that spreads over the body, particularly on the chest, face, and head, typically accompanied by flushing, perspiration, and often followed by a chill. In some instances, there are palpitations and a feeling of anxiety. Although these are characteristic features of a hot flash that make it an identifiable phenomenon, the magnitude and duration of any of these components can vary both within and among individuals, and not everyone experiences all of them. So some women flush, others do not; some sweat profusely, others hardly at all. Descriptions of hot flashes may also include pressure in the head or chest, a burning sensation, nausea, feelings of suffocation, and the inability to concentrate. Thus, just as the 28-day menstrual cycle is seen more in textbooks than in women, women's experiences of hot flashes are more variable than most textbook definitions.

Whether referred to as hot flashes, hot flushes, night sweats, or vasomotor symptoms (terms that are often used interchangeably), these episodic events can disrupt women's sense of well-being and can create problems for professional and social life.

### EPIDEMIOLOGY

Hot flashes primarily affect women who are in the transition to menopause or have become menopausal, whether naturally or due to medical intervention such as ovariectomy, chemotherapy, radiation, or medications that cause estrogen levels to fall. At other stages of the female reproductive life cycle, however, some women describe symptoms very similar to the hot flashes of menopause. A small percentage of premenopausal women report having hot flashes, as do women during pregnancy or in the early postpartum period.

Hot flashes may also be experienced by men upon abrupt loss of testicular function such as occurs following orchiectomy for prostatic or testicular cancer, following certain surgical procedures that compromise testicular function (2-5), or upon administration of GnRH agonists, which result in a fall in testosterone levels (6,7). Men who are hypogonadal due to other causes also can experience hot flashes (4).

Until relatively recently, most of the epidemiological studies of menopause had been conducted in North America and Europe (8-13). These studies found that the majority of women had at least some hot flashes. The prevalence of hot flashes is highest in the first two postmenopausal years, ranging from 58% to 93% in these studies, and lessens over time. In perimenopausal women, reports of hot flash prevalence range from 28% to 65%, and in premenopausal women, from 6% to 63%. Women with surgically induced menopause, at least for the first year postovariectomy, tend to have a relatively high prevalence of hot flashes, comparable to that of women in the first two years of natural menopause (see Tables 1 and 2 of ref. 14 for details of specific studies).

Hot flashes, although frequently occurring with menopause, are not universally experienced. Studies of menopause are now underway in countries around the world, and the data available thus far suggest that

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the high prevalence of hot flashes in Western societies is not the experience everywhere. Hot flashes have been reported in many cultures, including Indian, African, Native American, Japanese, Indonesian, Mexican American, Mayan, Thai, Filipino, and Chinese (15-24). But the prevalence of hot flashes within these cultures varies widely. Thus far, the most extensively studied non-Western group has been Japanese women, who report very few hot flashes (18,25). Mayan women in Yucatan, Mexico, do not report any symptoms at menopause other than menstrual cycle irregularity (21). These studies raise interesting questions. Are the physiological changes that are so characteristic of hot flashes in American women truly absent in other groups? Are they present but perceived differently? Are they, perhaps, not attributed to menopause? If absent or experienced by only a small percentage of the population, could this be due to diet, exercise patterns, or other cultural differences? Current research efforts may soon provide answers to some of these questions, and the results may generate leads to new methods of treatment. Increasingly, the patients in a medical practice come from a wide variety of cultural and religious backgrounds. It is therefore necessary to be aware of the menopausal symptoms that may be seen among women of other cultures, as well as to be sensitive to various cultural and medical traditions that might preclude a particular approach to treatment of hot flashes or include treatments not used by Western physicians.

### NATURAL HISTORY OF HOT FLASHES

The initial form of hot flashes and their pattern over time differ among women, but the physiological basis for these differences in hot flash patterns and presentations has yet to be definitively explained. For some women, hot flashes begin as menstrual cycles are becoming irregular: they tend to occur when menstrual cycles are absent and disappear when menstrual cycles resume. For others, hot flashes begin when menstrual cycles are still regular, which may be well before menopause. There are also instances in which hot flashes first begin several years after menopause (14). Few investigators have asked about the age and menstrual cycle status at which hot flashes begin, but those who have asked report that for a majority of women hot flashes begin prior to menopause (12,14,26).

The frequency, intensity, and duration of individual hot flash episodes vary both within and among individuals. Hot flashes may occur once a month or as often as every half hour. Most women with hot flashes have them infrequently, but about 10% to 15% of women have very frequent, severe hot flashes (14). Women with frequent hot flashes often have relatively consistent patterns of hot flashes, at least in the short-term.

Over months or years, however, an individual's hot flash pattern may change. In many cases hot flashes first occur at night and eventually occur during the day as well. Generally, hot flashes tend to become less frequent over time; however, for some women, they continue at frequent intervals until well into old age (14,27). The intensity of hot flashes can range from mild to very intense, over the course of one day, from day to day, or in different seasons. An individual hot flash episode typically lasts 3 to 6 min, although it can be of shorter duration, and on occasion a hot flash can last for more than 30 min.

The period of time over which hot flashes are most often experienced is 6 months to 2 years; however, women can have hot flashes for 10, 20, or even 40 years (14,26,28). Adequate data on the natural course of hot flashes is lacking because most investigators have not asked women across the life cycle whether they are having hot flashes. Most often excluded are women in their seventies and eighties; it had been assumed, incorrectly, that they would no longer have been experiencing hot flashes.

Although hot flashes often occur spontaneously with no observable trigger (particularly during sleep), some women report specific precipitating factors for their hot flashes. Psychological stress is often cited, as are hot weather (particularly hot, humid weather), a confining space, caffeine, alcohol, and spicy foods (14,29,30).

Few studies have examined factors that might predispose women to hot flashes. No significant association has been found between the occurrence of hot flashes and sociodemographic variables such as employment status, social class, age, or marital status (13). Women with hot flashes are not distinguishable from those without hot flashes by age at menarche, number of pregnancies, or previous medical problems (31). One factor that has been shown to relate to the occurrence of hot flashes in menopausal women is mean body weight and percent ideal body weight. Asymptomatic women had significantly higher mean body weight, percent ideal body, and total circulating estrogen levels, than women with hot flashes (32). Recent data from a prospective study of the natural menopausal transition indicate that women with longer perimenopausal periods were more likely to report hot flashes than were those with a short perimenopausal period (51% as compared with 39%) (33). Further research will determine whether factors such as genetics, diet, and exercise will be found to influence hot flashes.

### PHYSIOLOGY OF HOT FLASHES

Thermoregulatory and cardiovascular changes that accompany a hot flash are now well documented.

Characteristic patterns exist amid a range of individual variability (Fig. 1, Table 1). Knowledge of the time sequence of physiological changes during a hot flash has grown incrementally as researchers have measured additional parameters. It is now frequently reported that many women have a premonition of an impending hot flash (an aura), which they distinguish from the hot flash itself. This prodromal feeling is often described as one of disease, anxiety, a tingling sensation, or pressure in the head (14). During this period immediately prior to the onset of a hot flash (approximately 5 to 60 sec), heart rate and cutaneous blood flow begin to increase (34,35).

At the start of a hot flash typically there is a sudden onset of sweating primarily on the upper body but measurable all over the body, as indicated by a rapid drop in skin resistance (increase in skin conductance) (35,36). The main sensation is one of intense heat, although internal body temperature never rises above normal. As cutaneous blood flow increases (34,35) and heart rate continues to accelerate (4 to 35 beats/min) (34,35,37), skin temperature rises, particularly that of

the fingers and toes (1 to 7°C) (1,35,38,39), and sweating continues. Evaporative cooling may cause the temperature of the wet skin to drop, particularly on the chest and forehead, where sweating tends to be profuse (35). Heart rate and skin blood flow peak within about 3 min of hot flash onset (34,35). To relieve their discomfort, women initiate a variety of behavioral measures to dissipate heat. The vasodilation, sweating, and behavioral responses result in heat loss and a drop in internal temperature (0.1 to 0.9°C), which reaches a nadir about 5 to 9 min after the onset of the hot flash (35,36). If there has been significant heat loss and core temperature has dropped, there may be the sensation of a chill, or even some shivering as the hot flash resolves. Vasoconstriction, behavior to promote warming, and at times an increase in metabolic rate due to shivering, facilitate the return of body temperature to normal. Skin temperature gradually declines to its pre-hot-flash level. This can take 30 min or more, depending on skin and ambient temperatures. No change in blood pressure has been found in association with a hot flash (34,37,40). Although sweating and the

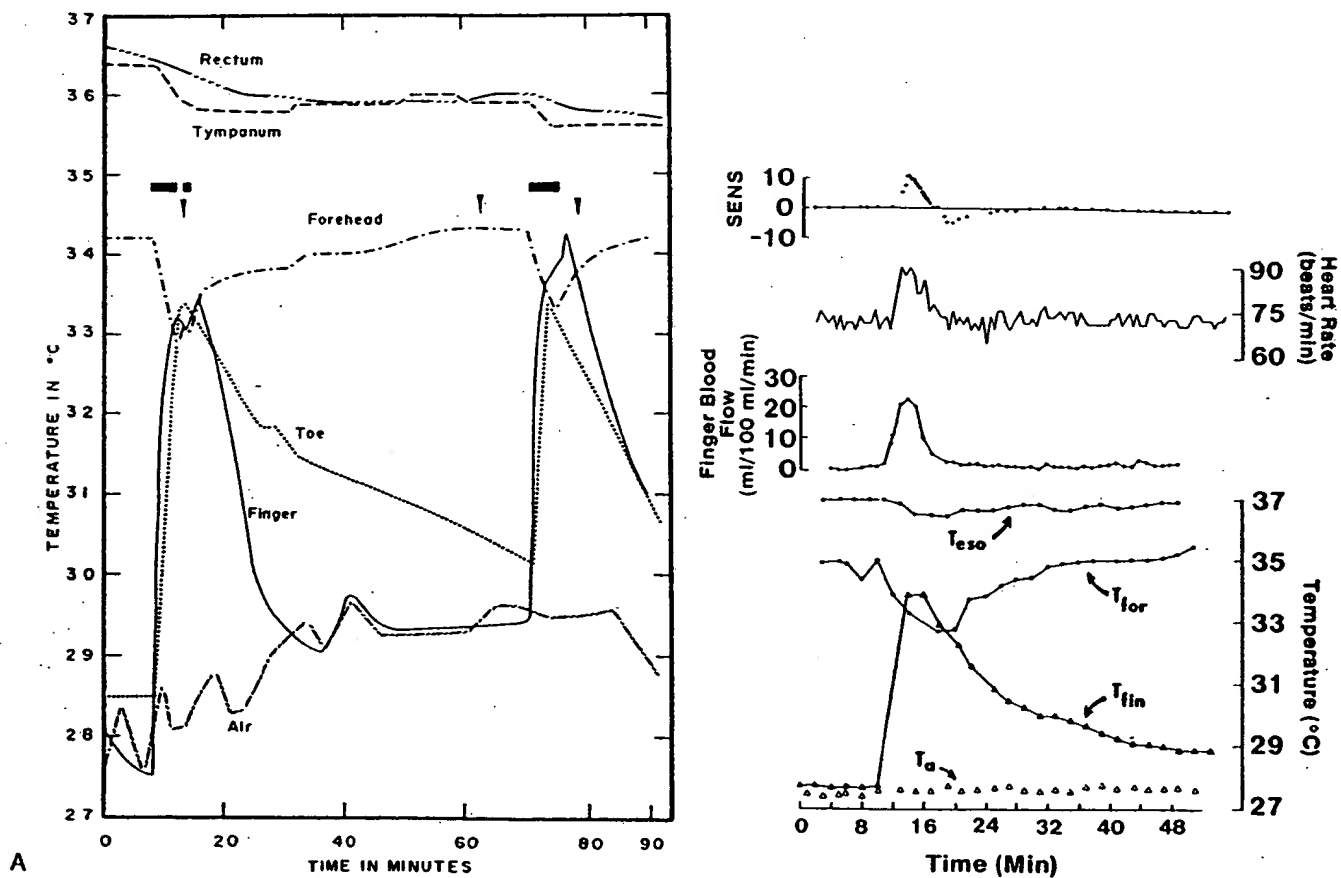


FIG. 1. A: Temperature responses to two spontaneous flashes (■) and evoked flash (■). ↓, Finger stab for blood sample. Nude. (From ref. 1, with permission.) B: Thermoregulatory and cardiovascular changes during a typical hot flash at an ambient temperature of 28°C. Subjective sensation, blood flow (finger), heart rate (30-sec averages), skin resistance (chest), internal body temperature (vagina), and skin temperatures (forehead, finger) are depicted. (From ref. 14, with permission.)

TABLE 1. Clinical picture of a hot flash

Symptom	Description
Sensation	Sudden feeling of heat and sometimes anxiety
Heart rate	Increases (5–35 bpm), sometimes felt as palpitations
Cutaneous blood flow	Increases; observed as flushing
Finger skin temperature	Rises rapidly (1–7°C) and slowly declines after hot flash ends
Sweating	Often profuse, with rapid onset; rate of evaporation depends on ambient humidity and temperature
Core temperature	Decreases (0.1–0.9°C) several minutes after hot flash starts; sometimes felt as a chill at end of hot flash
Sleeping problems	Increase in nighttime awakenings associated with hot flashes (night sweats)

perception of heat are most intense on the upper body, the temperature of the toes increases concomitantly with finger temperature, and sweating may occur over the lower body as well (1,35), demonstrating that a hot flash is a generalized physiological phenomenon.

The subjective perception of the intensity of a hot flash is likely due to a combination of factors, including the associated sweating and increased heart rate, and probably involves other ill-defined sensations. The sensation of hot flash intensity is not a direct func-

tion of absolute skin temperature or the change in skin temperature during a hot flash, since the degree to which finger skin temperature increases during a hot flash is inversely proportional to the baseline skin temperature before the hot flash (Fig. 2) (35,36,41). The more distal the site, the lower skin temperature is likely to be initially and, therefore, the greater the potential for seeing an appreciable rise in skin temperature during a hot flash. As a result, in many studies finger temperature is used as an objective indication of a hot flash. This measurement works well in cool ambient temperature, but less well in warm ambient temperatures when baseline skin temperature already may be high.

## ENDOCRINOLOGY OF HOT FLASHES

### Estrogen

Given the long-known association of hot flashes with the onset of menopause and of menopause with a drop in circulating levels of estrogen, investigators have sought to determine whether there might be a relationship between estrogen and hot flashes. In early studies, no correlation was found between estrogen levels in the blood and the presence or absence of hot flashes in postmenopausal women (42–45), nor were any acute changes in estradiol or estrone associated with individual hot flashes (46). In other studies, postmenopausal women with severe hot flashes were found to have lower levels of circulating estrone and estradiol than did asymptomatic women (Fig. 3) (32,47,48). More specifically, Erlik et al. (32) found the fraction of estradiol not bound to sex hormone-binding globulin (SHBG) to be significantly higher in asymptomatic women than in women with hot flashes. Although estrogen does not appear to trigger individual hot flashes, levels of plasma estrogens do play some, as yet undetermined, role in the etiology of hot flashes.

Hot flashes involve more than just the presence of low plasma estrogen levels. Throughout the postmenopausal period, estrogen levels remain low, yet some women never have hot flashes, while for others, hot flashes may occur only sporadically or may soon cease. In other situations in which estrogen levels are low, such as in prepubertal girls or women with anorexia nervosa, hot flashes are not reported. Furthermore, hot flash-like episodes are reported during pregnancy (particularly the last trimester), when plasma estrogen level becomes particularly high (F. Kronenberg, unpublished data). Hot flashes also occur in premenopausal women during pituitary suppression with a gonadotropin-releasing hormone (GnRH) agonist, when serum estradiol concentration is maintained at premenopausal levels (49).

What seems to be more important than levels of es-

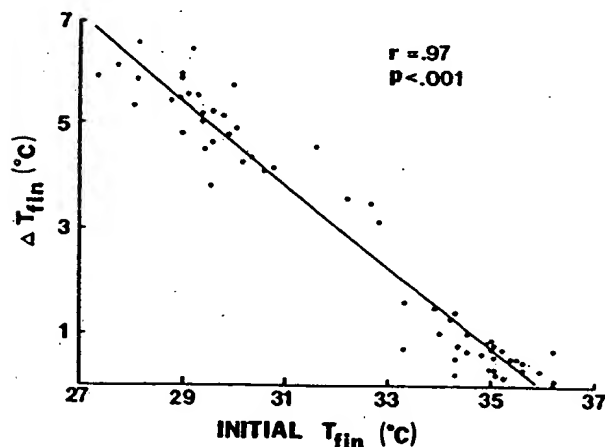


FIG. 2. Relationship between the maximum increase in finger temperature ( $T_{fln}$ ) during a hot flash and the finger temperature immediately before the hot flash (INITIAL  $T_{fln}$ ). (From ref. 85, with permission.)



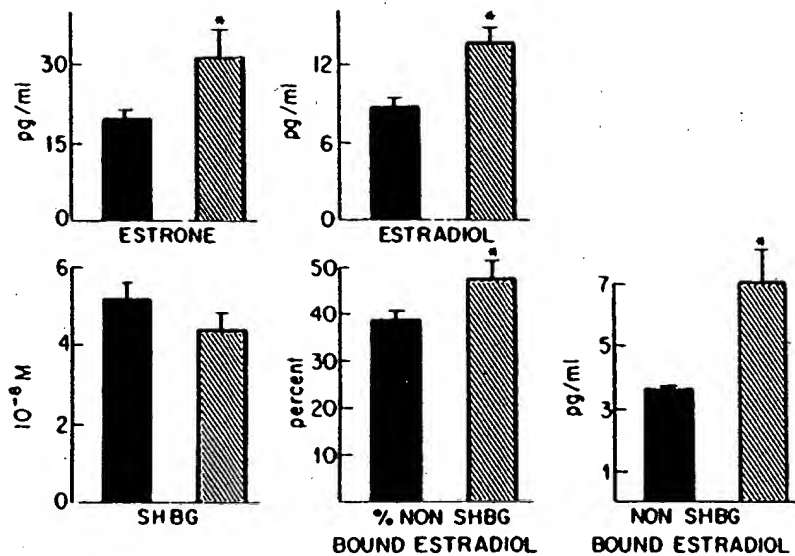


FIG. 3. Mean  $\pm$  SE levels of estrone, estradiol, sex hormone-binding globulin (SHBG), percent non-SHBG-bound estradiol, and non-SHBG-bound estradiol in 24 women with hot flashes (solid bars) compared with 24 asymptomatic subjects (striped bars). Asterisk indicates significantly different from asymptomatic subjects. (From ref. 32, with permission.)

trogen per se is a drop in estrogen concentration. For example, the abrupt onset of hot flashes following ovariectomy (42,50) or the administration of GnRH analogues, which cause plasma estrogen to fall (51,52), support this contention. So does the observation that postmenopausal women with gonadal dysgenesis (Turner's syndrome) who have never had normal adult estrogen levels do not experience hot flashes unless they are first prescribed, and then withdrawn from, estrogen (38,53). Estrogen therapy generally ameliorates hot flashes, and upon discontinuation of estrogen treatment, they often return. There have been no reports to indicate whether women with hot flashes have a more precipitous natural decline in estrogen than do those who never have hot flashes.

Hot flashes have also been reported by men upon acute withdrawal of testosterone, such as after total orchiectomy (2,3). The decline in testosterone as men age is far more gradual than the decline in estrogen that occurs in women, which may be the reason that hot flashes are not frequently reported in men. Thus a sudden decrease in sex steroids in either women or men can precipitate hot flashes.

The specific role of estrogen in the etiology of hot flashes remains to be fully understood. In addition to its effect on reproductive tissues, estrogen influences thermoregulatory, neural, and vascular functioning. The firing rate of thermosensitive neurons in the preoptic area of the hypothalamus in response to thermal stimuli can be modulated by estrogen (54). Estrogen also influences internal body temperature, although the direction of the effect differs between studies (55,56). The responsiveness of vascular smooth muscle to vasoactive substances such as epinephrine and norepinephrine is affected by estrogen (57) and has been shown to be greater in women with hot flashes than those without hot flashes (58). Thus estrogen may

have peripheral as well as central effects that are important to hot flash physiology.

#### Luteinizing Hormone (LH)

In addition to the study of estrogen's relationship to hot flashes, the role of gonadotropins has been examined as well, since gonadotropin levels become elevated at menopause. However, high gonadotropin levels are not the direct cause of hot flashes, since (a) LH level remains high postmenopausally while hot flashes tend to lessen, (b) no differences in absolute levels of LH have been found between women with and without hot flashes (59), and (c) hot flashes can be diminished by estrogen doses insufficient to reduce LH levels in the blood (60). Furthermore, when anti-gonadotropins such as danazol or GnRH analogues are given to women with endometriosis, hot flashes often occur despite a decline in LH level (60).

Thus absolute LH level has provided little insight into hot flash etiology. When serial blood samples were drawn, however, LH in the peripheral circulation was found to exhibit a temporal correlation with hot flashes (Fig. 4); most hot flashes are accompanied by an increase in LH (38,39). The correspondence of LH pulses with hot flashes led to speculation that LH might be responsible for the initiation of hot flashes. But it was soon evident that a pulse of LH was not a necessary concomitant of hot flashes. Hot flashes can occur in women who have no episodic LH release such as those with hypophysectomy (Fig. 5) (61,62), in pre- or postmenopausal women in whom pulsatile LH release has been suppressed by treatment with a GnRH agonist (Fig. 6) (51,63,64), and in women with pituitary insufficiency and hypoestrogenism (62). Ravnkar et al. (65) found there to be a similar number of LH

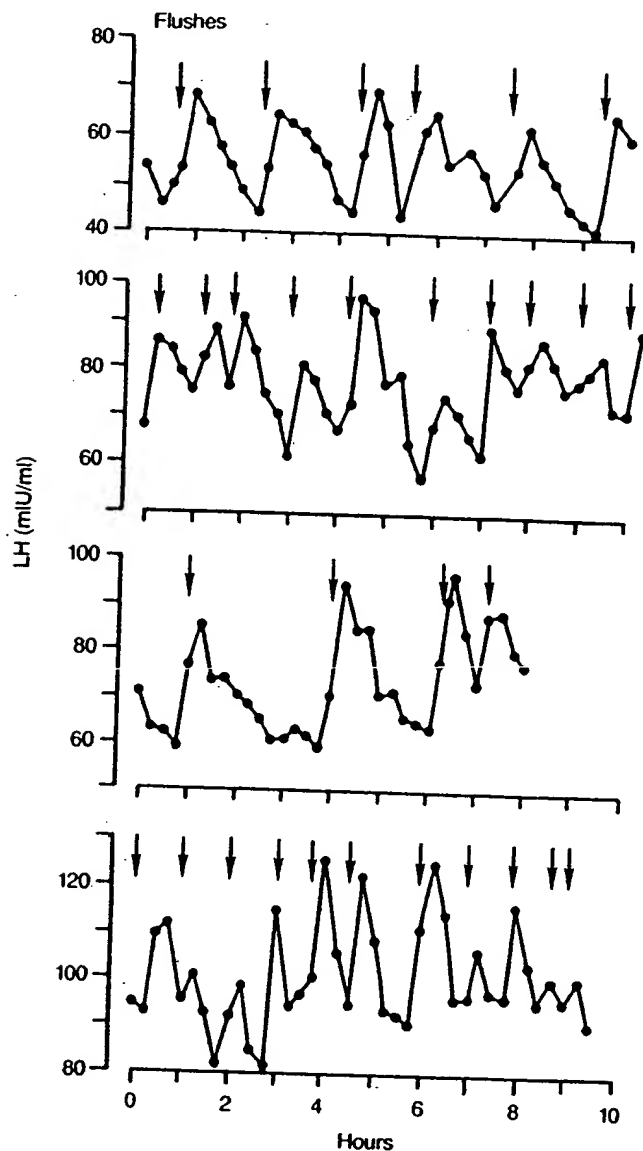


FIG. 4. Pattern of pulsatile LH release and associated menopausal flush episodes. Arrows indicate flush onset. Each part illustrates a separate 8- to 10-hr study in which blood samples were obtained at 15-min intervals. Note that each flush is synchronized with an LH pulse. (From ref. 38, with permission.)

pulses in women with or without hot flashes. Thus LH secretion per se is not the immediate trigger of hot flashes.

#### Gonadotropin-Releasing Hormone (GnRH)

Since pulses of LH were not directly responsible for initiating hot flashes, but they were associated with hot flashes, it was thought that perhaps hot flashes might be initiated at the hypothalamic level and involve the releasing factor for LH. Immunoreactive GnRH was measured in the peripheral circulation of

women with and without hot flashes and discovered to be elevated prior to the LH pulses observed with hot flashes. Women with hot flashes also had higher mean plasma immunoreactive GnRH levels than did asymptomatic women (65). Yet women with defects in GnRH synthesis or release (isolated gonadotropin deficiency), who received estrogen treatment, had hot flashes when they were withdrawn from estrogen (66). Furthermore, when GnRH receptors were blocked with a long-acting GnRH antagonist in women who never had hot flashes, although LH pulses were abolished, these women experienced hot flashes for the first time (51). Thus episodic GnRH release is not necessary for hot flashes to occur.

#### Other Endocrine Studies

Circulating epinephrine and norepinephrine have been measured during hot flashes by several investigators with conflicting results. Casper et al. (38) found no change in epinephrine or norepinephrine in association with individual hot flashes. Given the 2- to 3-min half-life of epinephrine and norepinephrine (67), Kronenberg et al. (35) sampled at more frequent intervals and found a significant increase in plasma epinephrine and a decrease in norepinephrine during hot flashes (Fig. 7). Mashchak et al. (68) found epinephrine to increase but saw no change in norepinephrine levels.

Other substances that have been measured in the peripheral circulation during hot flashes are listed in Table 2. Circulating  $\beta$ -endorphin,  $\beta$ -lipotropin, and adrenocorticotrophic hormone (ACTH) increase in association with hot flashes (Fig. 8) (69,70), as do cortisol, dehydroepiandrosterone (DHEA), and androstenedione (46,69,70) (Fig. 9). The peak levels of most of these substances are reached after the subjective hot flash has ended. Prolactin level did not change during hot flashes. Once again, no causal relationships have been found.

#### HOT FLASHES AND SLEEP

One of the primary complaints of women with hot flashes is that their sleep is disrupted. They may awaken several times during the night, drenched in sweat, necessitating a change of bedding and clothes. Erlik and co-workers (71) used electroencephalography (EEG) to demonstrate that nocturnal awakenings in postmenopausal women with hot flashes were correlated with the occurrence of the hot flashes (Fig. 10). Sleep efficiency is lower and latency to REM (rapid eye movement) sleep is longer in women with hot flashes compared to those with no hot flashes (72). This disturbed sleep often leads to fatigue and irritability during the day. The frequency of awakenings and

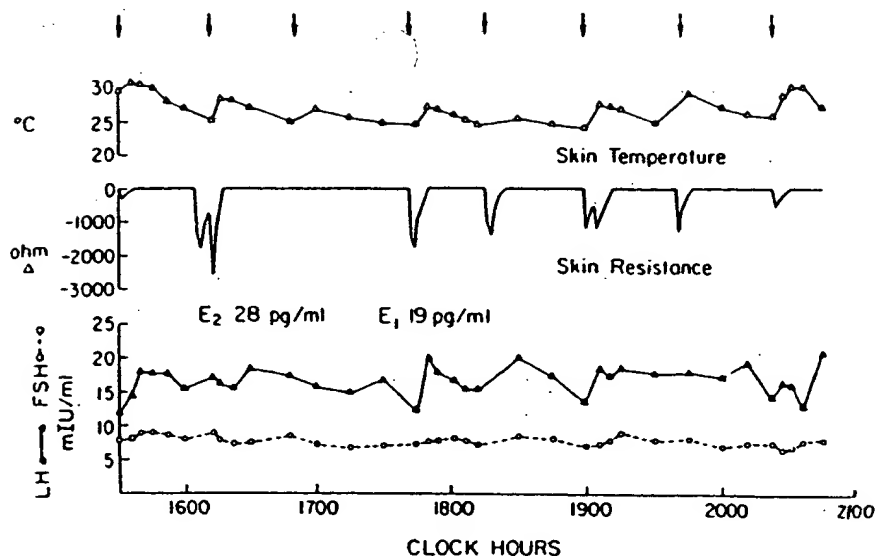


FIG. 5. Serial measurements of skin temperature, skin resistance, and serum LH and FSH levels in a woman after hypophysectomy (patient 1). Skin resistance changes are depicted at 1-min intervals as the change in ohms from the baseline immediately preceding the episode. Arrows mark the onsets of subjective hot flushes. E<sub>2</sub>, estradiol; E<sub>1</sub>, estrone. (From ref. 62, with permission.)

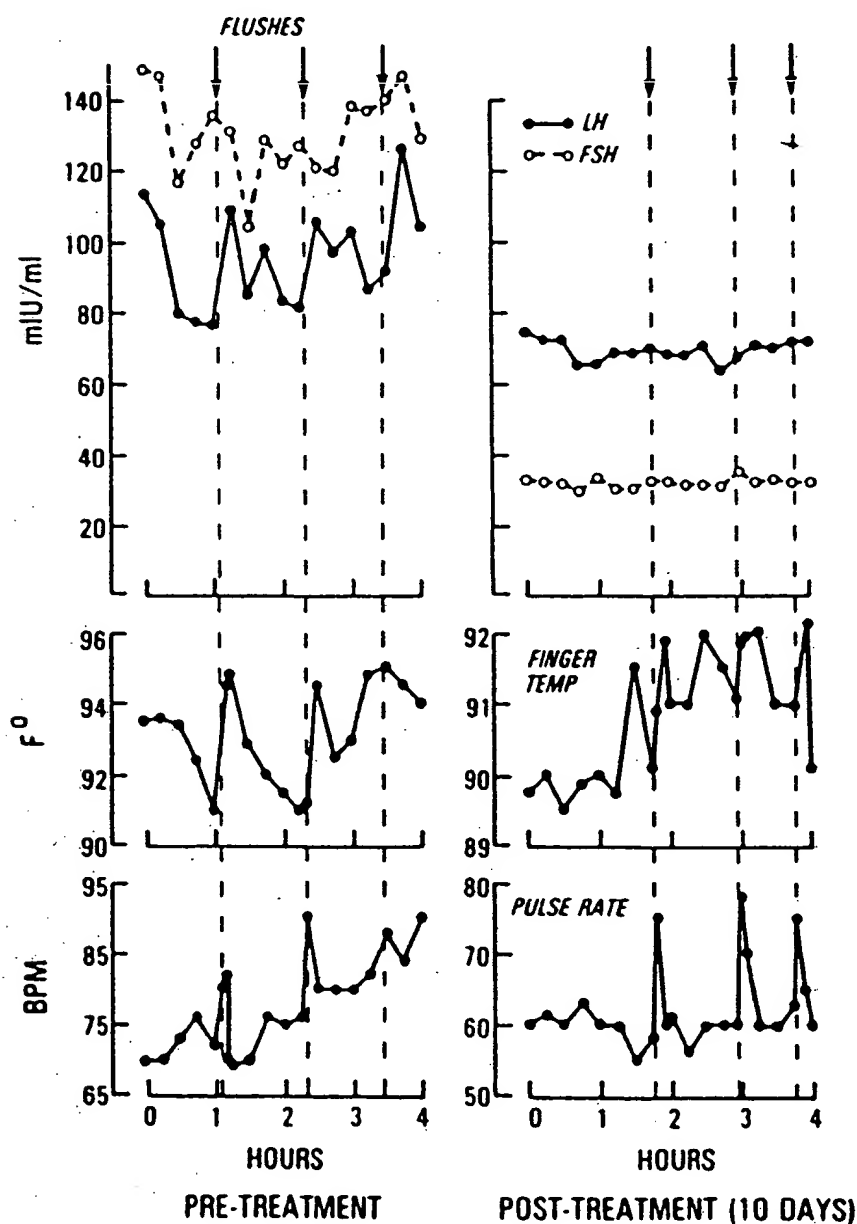


FIG. 6. Changes in finger temperature (°F) and pulse rate (beats/min) in association with flush episodes (arrows) and serum concentrations of LH (●-●) and FSH (○-○) in a representative study of one hypogonadal subject before and after 10 days of daily LRF-Ag administration (50 μg sc). (From ref. 63, with permission.)

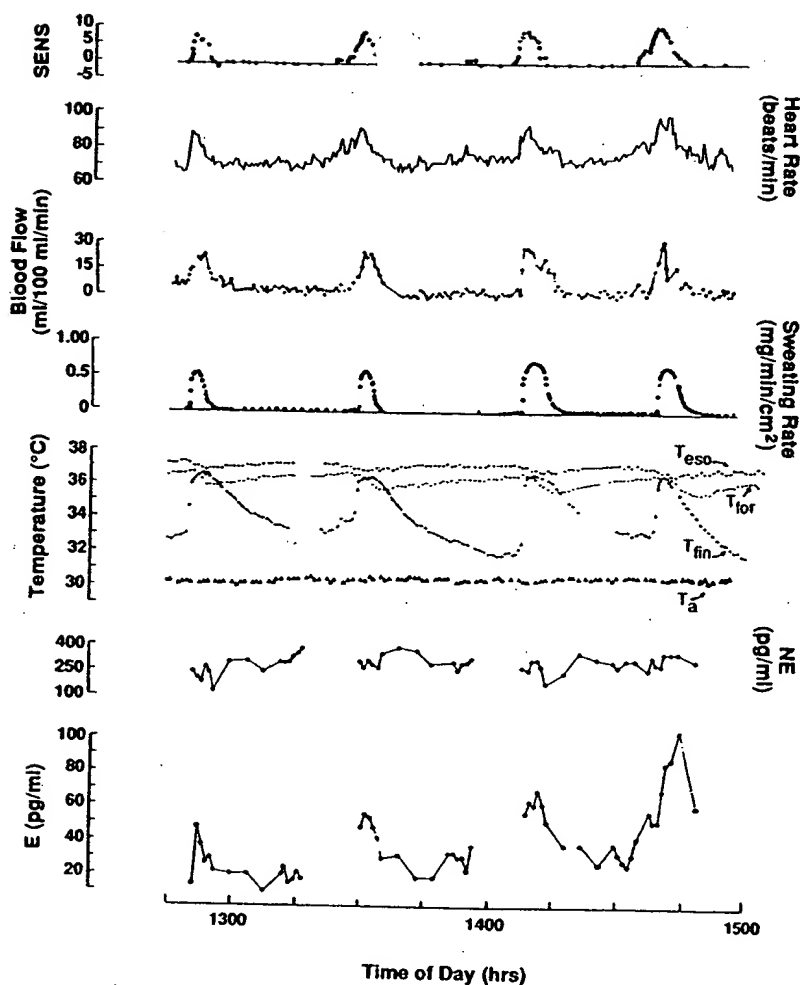


FIG. 7. Pattern of cardiovascular, thermoregulatory, and endocrine changes for four consecutive hot flashes over a 2-hr period. Changes in sensation (SENS), heart rate, blood flow (finger), sweating rate, temperatures (esophageal, forehead, finger, and ambient), norepinephrine (NE), and epinephrine (E) are depicted. (From ref. 85, with permission.)

TABLE 2. Hormone changes during hot flashes

Substance	Response	Reference
LH	Increase	35,38,39,46,68,69,120,121
FSH	No change	39,46,68,120
GnRH	Increase	38,69
Estradiol	Increase	65
Estrone	No change	46
Dehydroepiandrosterone	No change	46
Androstenedione	Increase	46
Progesterone	Increase	46
Epinephrine	Slight increase	46
Norepinephrine	Increase	35,68
	No change	38,121
	No change	38,68,120
	Decrease	35
Dopamine	Increase	121
Prolactin	No change	38,121
Cortisol	No change	38,46,120
	Increase	46,69,121
ACTH	No change	122
$\beta$ -Endorphin	Increase	46,69
$\beta$ -Lipotropin	Increase	46,69
Neurotensin	Increase	69
Growth hormone	Increase	123
TSH	Increase	46
Glucose	No change	46
Glucagon	No change	121
Insulin	No change	121
	No change	121

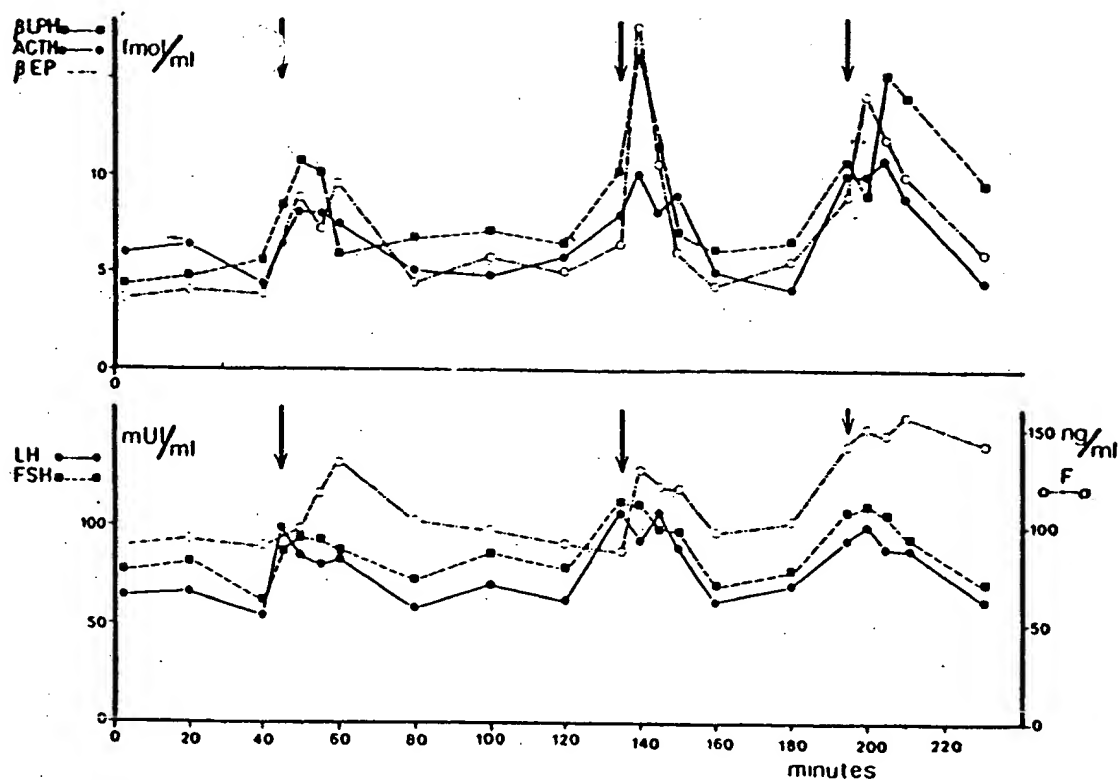


FIG. 8. Plasma levels of adrenocorticotropin (ACTH),  $\beta$ -lipoprotein ( $\beta$ -LPH),  $\beta$ -endorphin ( $\beta$ -EP) (top) and luteinizing hormone (LH), follicle-stimulating hormone (FSH), and cortisol (F) (bottom) in subject M.M. during observation period. Arrows indicate onset of hot flashes. (From ref. 69, with permission.)

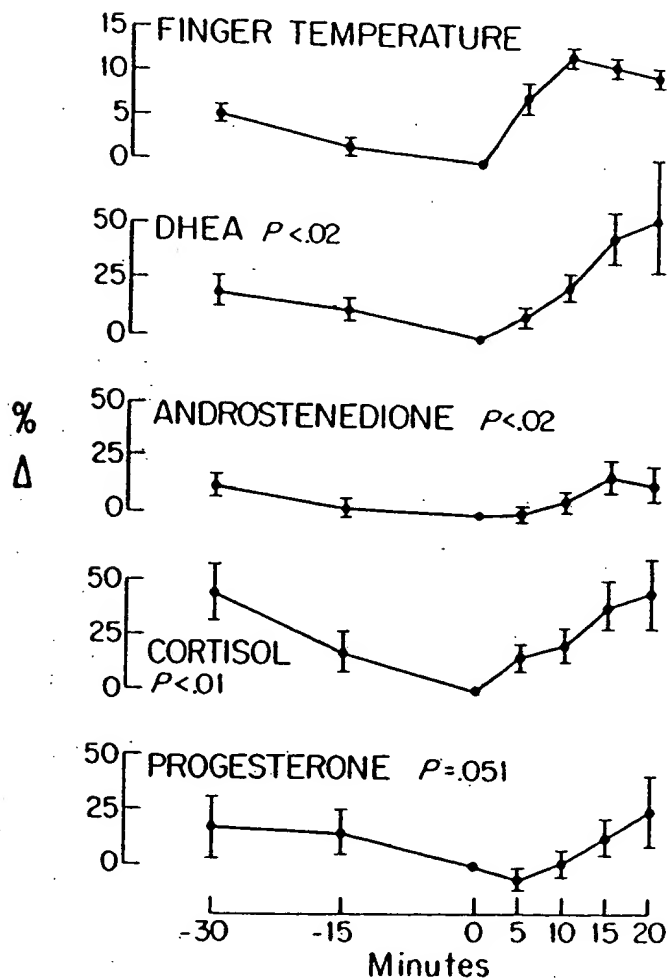
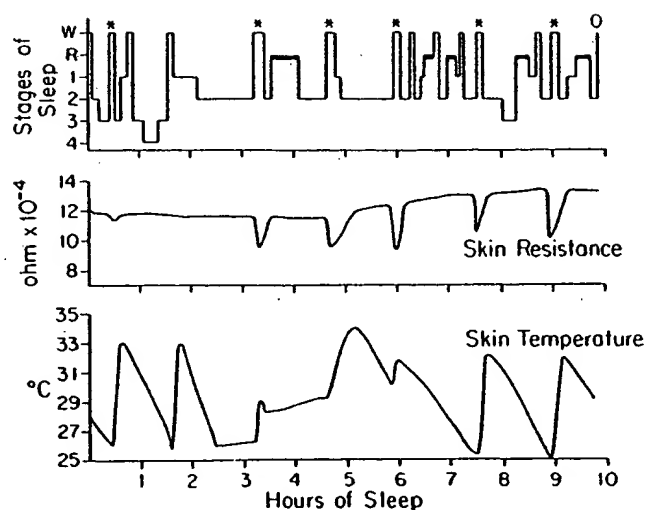
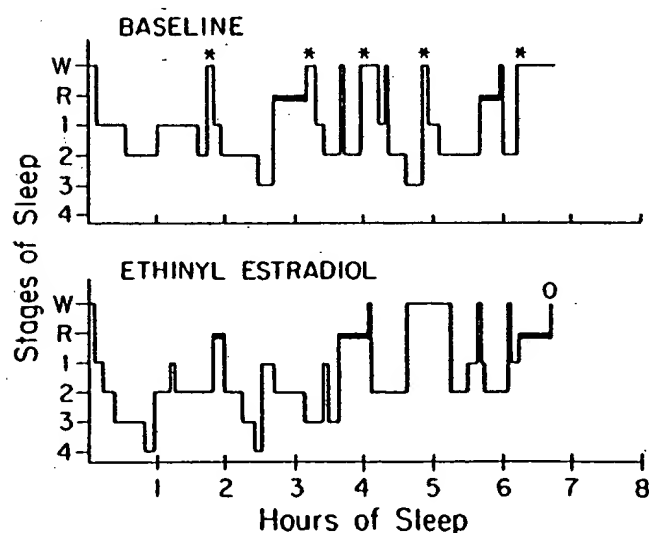


FIG. 9. Mean percent change of finger temperature and serum DHEA,  $\Delta$ , F, and P levels before and after objective flashes. (From ref. 46, with permission.)



**FIG. 10.** Sleepgram and recordings of skin resistance and temperature in postmenopausal subject with severe hot flushes. Each asterisk marks occurrence of objectively measured hot flush. Open circle indicates arousal of patient by investigator at end of the study. (From ref. 71, with permission.)

of hot flashes are reduced with estrogen treatment (Fig. 11) (71,73,74). Sometimes, a woman may not consciously awaken from sleep (even though the EEG recording indicates momentary arousal), yet objective physiological measurement has documented the continuation of hot flashes throughout the night (Fig. 12). This sleep disturbance due to hot flashes is a primary motivator for women to seek medical advice and pharmacologic solutions. As is indicated later, a nonpharmacologic approach may also provide nighttime relief for some women.



**FIG. 11.** Sleepgrams measured in symptomatic patient before and after 30 days' administration of ethinyl estradiol, 50  $\mu$ g four times daily. (From ref. 71, with permission.)

## AMBIENT TEMPERATURE AND HOT FLASHES

Many women find that their hot flashes are worse in warm weather. To relieve the discomfort of hot flashes, women may stand in front of an air conditioner or refrigerator, wear loose, light, nonsynthetic clothing, or, on cool nights, open windows. Yet scant research exists on the effect of ambient temperature on hot flashes. Hot flash frequency has been found by some investigators to correlate positively with outdoor temperature (75,76), while others found no relationship to exist (29,30). However, what has long been reported anecdotally, and in some uncontrolled thermal environments, has now been demonstrated under controlled temperature conditions. That is, ambient temperature does significantly influence both the frequency and intensity of hot flashes. In a cool environment (19°C) women had significantly fewer and less intense hot flashes than in a warm (31°C) environment (77) (Fig. 13). Cooling room temperature may therefore be one way in which women can reduce their hot flashes, particularly during sleep.

## ETIOLOGY

Several hypotheses to explain the mechanism underlying hot flashes have been put forth (66,78–81). These hypotheses are based on data obtained primarily from studies of women with hot flashes in which substances measured in the peripheral circulation have been found to change in association with the hot flashes, or from observations on the success of various drugs in treating hot flashes. The hypotheses discussed most widely involve  $\alpha$ -adrenergic mechanisms, endogenous opioid peptide, and GnRH. There have been a number of detailed reviews and critiques of the proposed models and theories to explain hot flashes (78,79,82–84). The definitive explanation still eludes us.

The hormonal milieu is obviously relevant to the occurrence of hot flashes. However, measuring the endocrine concomitants of hot flashes either in terms of mean hormone levels or episodic changes has not uncovered the initiating factor responsible for triggering a hot flash.

The sequence of events that characterizes a hot flash appears to be the result of a perturbation of the brain's thermoregulatory center located in the hypothalamus, activating mechanisms of heat loss (vasodilation, sweating, and behavioral adjustments) at hot flash onset, and heat conservation (vasoconstriction, behavioral changes, and shivering) at the termination. The combination and sequence of physiological and behavioral responses during a hot flash suggest that the phenomenon involves the coordinated action of the thermoregulatory system. The body responds as it

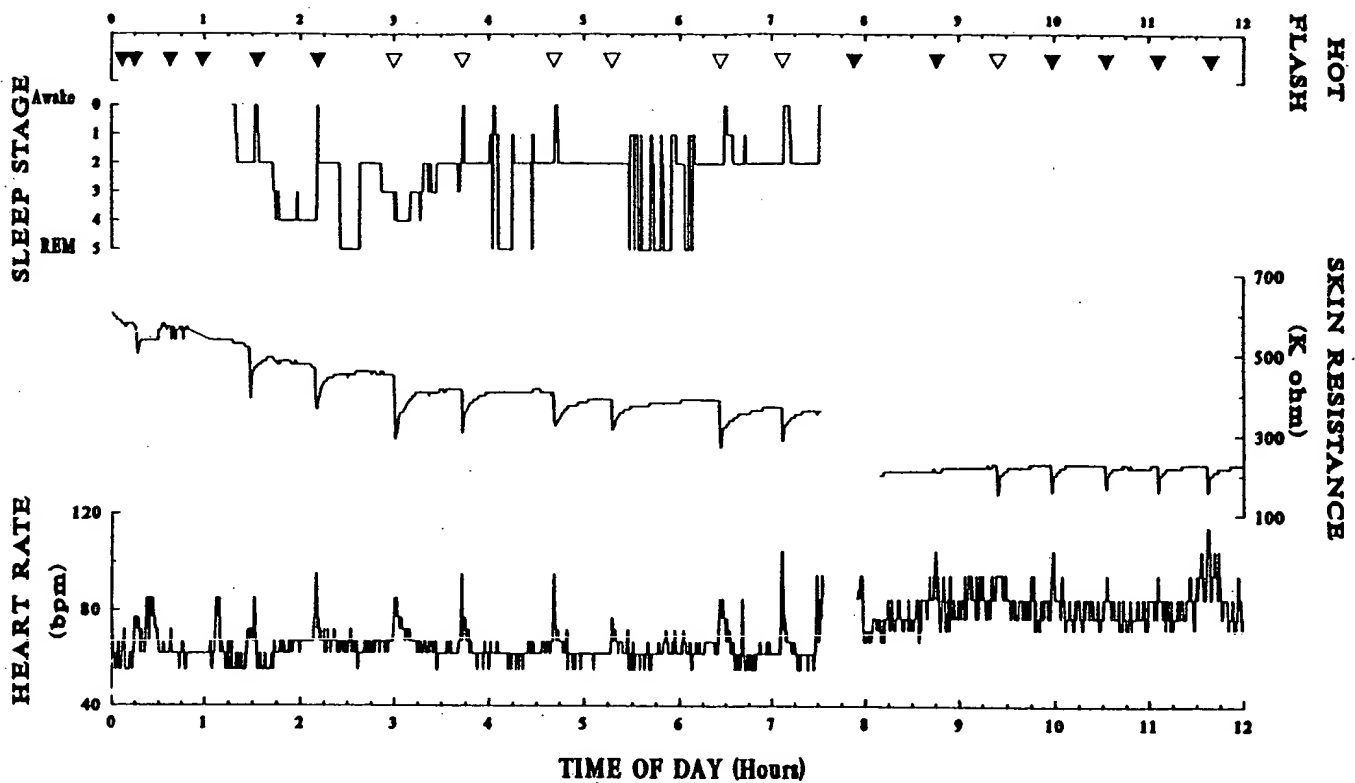


FIG. 12. Pattern of sleep stages, skin resistance, and heart rate for a 12-hr period (subject #A-10). The *solid triangles* (▼) indicate reported hot flashes; *open triangles* (▽) indicate unreported hot flashes. Sleep stages 1 through 4, NREM sleep; stage 5, REM (rapid eye movement); absolute clock time on the *abscissa*. The sudden drop in skin resistance at about 7:00 a.m. is due to a change of skin resistance electrodes. This subject went to bed shortly after 1:00 a.m. and awoke at about 7:30 a.m. (From ref. 14, with permission.)

would to dissipate excess heat in situations of overheating or at the breaking of a fever. Since there is no elevation of internal temperature associated with a hot flash, however, the responses are consistent with the hypothesis that a hot flash involves a transient downward resetting of the body's thermoregulatory set-point (36,85). In other words, at the start of a hot flash there is a sudden drop in set-point temperature. Since the body would then be warmer than this new set-point, the thermoregulatory system acts appropriately to cool the body. As a result, internal temperature falls. The set-point then returns to normal, and heat conservation mechanisms act to return body temperature to normal. This entire process is analogous to what happens during a fever, but the change in set-point is in the opposite direction than during fever (36,85). Pyrogenic substances can raise the set-point temperature and initiate the thermoregulatory responses that result in a fever (86). What remains unknown is precisely what causes the hypothalamic resetting during a hot flash.

Possible candidates include endocrine and neuroendocrinological substances. Reproductive hormones modulate the functioning of the thermoregulatory sys-

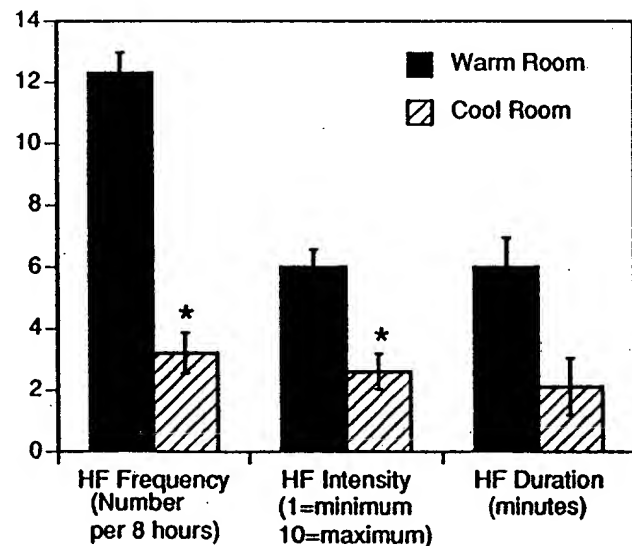


FIG. 13. Mean frequency, intensity, and duration of hot flashes at warm (31°C) versus cool (19°C) ambient temperatures  $\pm 1$  SEM. \* $p < 0.05$ . The units of the y-axis vary with parameter, as indicated. (From ref. 77, with permission.)

tem (85), as do opioid peptides (87–89), which also modulate and are influenced by reproductive hormones (90–92). Further delineation of the relationship between sex steroids, opioid peptides, and thermoregulatory function is necessary.

A coherent hypothesis should be able to accommodate the hot flash-associated thermoregulatory and neuroendocrine responses, and be able to explain among other things: (a) why different individuals experience hot flashes at different frequencies and for varying lengths of time, and why some women never get hot flashes; (b) why hot flashes begin in some women just hours after ovariectomy; (c) why some women sweat while others do not; (d) why priming with estrogen is necessary before hot flashes can occur (no hot flashes are seen in prepubertal girls, or women with gonadal dysgenesis before treatment with estrogen); (e) the similar phenomenon of hot flashes in women and men following a reduction in estrogen in women or testosterone in men; (f) the observations that drugs such as clonidine have been demonstrated to eliminate the sensation of hot flashes, while pulses of finger temperature and LH remain. Are there invariant components of a hot flash that are always measurable, independent of environmental conditions, age, or sex? A resolution of these questions awaits additional research, and perhaps an animal model that more closely resembles the human female in terms of both endocrine and thermoregulatory functioning.

### WHY ARE HOT FLASHES A PROBLEM?

If hot flashes occur only sporadically, they are not likely to be disruptive or even much greater than a nuisance. But for those women with many hot flashes throughout the day, every day, hot flashes can be periodically disabling, physically draining, and can impact negatively on work, family, and social relationships. When hot flashes disturb sleep every night, the consequences can be debilitating. Some women choose to avoid touching, hugging, or sexual activity because the skin-to-skin contact may bring on a hot flash.

Profuse sweating during a hot flash is one of the most bothersome complaints; it can be an embarrassment, particularly at work or in social situations. It may even require a change of clothing, which is not always possible or convenient. Women with severe hot flashes describe their lives as a constant struggle to achieve thermal comfort. They must adjust their behavior (such as wearing layers of clothes for easy removal, shunning synthetics for natural fibers, or carrying a fan), or they attempt to alter their immediate environment by turning on the air conditioner, opening windows, going outside if the weather is cool, or staying inside on hot humid days.

### DIAGNOSIS

Most women who present with hot flashes will be perimenopausal or recently postmenopausal. Therefore age and menstrual history (menstrual cycle irregularity, oligomenorrhea or amenorrhea) give strong indications that these are menopausally related hot flashes, as do other complaints suggestive of low estrogen, such as vaginal dryness and its sequelae. During the perimenopausal period, hot flashes may come and go. Menstrual cycle irregularity may correspond with these fluctuating episodes. If women are still menstruating regularly when hot flashes first occur, they may not recognize that the episodes of feeling hot and sweating are actually hot flashes. Thus there may be many years of hot flashes prior to menopause. And hot flashes may continue long into the postmenopausal years, and sometimes throughout a woman's lifetime.

In the few cases where diagnosis of hot flashes is unclear, it may be of value to measure plasma follicle-stimulating hormone (FSH) and LH, since they are both elevated in menopausal women. However, particularly during the perimenopause, levels of these hormones fluctuate. So multiple measurements would have to be made. FSH is better diagnostically than LH since the increase in circulating LH tends to lag behind the rise in FSH. Estradiol is not a particularly good indicator on which to base diagnosis in women of pre- and perimenopausal ages.

Several conditions share some clinical features with hot flashes, particularly the flushing and sweating. These include hyperthyroidism, panic attacks, carcinoid syndrome, pheochromocytoma, and niacin flush.

### MANAGEMENT

Many women can make adjustments necessary to cope with their hot flashes if they are provided with adequate information and support. Women can experience a wide range of sensations during hot flashes. This may be upsetting if they are unaware of what to expect. Many of the worries of women with hot flashes can be allayed if they are informed of what is and what is not known. They could be told, for example, that no one can predict exactly how long their hot flashes will last or, therefore, the necessary duration of treatment. It is also important to convey that hot flashes may recur when treatment is ended.

The initial stages of management should include a determination of the level of impact of the hot flashes and an assessment of how the woman has been coping with them. Precipitating factors such as hot drinks, alcohol, caffeine, or hot environments should be identified and avoided. Stresses at home or in the workplace may also make hot flashes even more difficult to cope with.



Many women try to control their hot flashes by modifying their environment or behavior before consulting a physician. They change room temperature, wear light, layered clothing, and try vitamins or dietary changes that have been suggested to them. For some, these attempts may be effective and the hot flashes may become less intense or less frequent. While for others, nothing they do has any impact on their relentless hot flashes. When knowledge, prescription, and behavioral changes prove insufficient, women may ask about hormone therapy.

### Pharmacologic Preparations

The available therapies do not "cure" hot flashes; rather, they provide symptomatic relief by making the hot flashes less frequent and/or less intense, or sometimes by eliminating them, at least for the duration of the treatment. If hot flashes return when treatment is stopped, it is not known whether the treatment just postponed the hot flashes, or whether the individual would have had hot flashes for that duration regardless of whether she had been treated. To minimize the recurrence of hot flashes, it is advisable to taper drug treatment over several weeks, rather than stopping suddenly. We do not know the mechanism by which hot flashes are reduced for any of the treatments discussed below.

When various hot flash therapies are compared with a placebo, the placebo often demonstrates considerable effectiveness. Therefore to best assess the efficacy of a treatment, it is necessary to conduct randomized, double-blind, placebo-controlled crossover studies. And, as it may take several weeks to effectively control hot flashes, studies must be of sufficient duration to adequately determine how well a particular treatment works.

### Estrogen

Estrogen administration is currently the most effective treatment for hot flashes. It has been used, albeit initially in the form of crude extracts, for almost 100 years. The rationale is based on the association of hot flashes with the decline in ovarian function at menopause rather than on the knowledge of the cause of hot flashes.

The effect of estrogen treatment on hot flashes is not usually immediate. The full benefit may not be realized until several months of therapy. When treatment is discontinued, the effect on hot flashes may persist for some time, depending on the type of estrogen or route of administration. For example, conjugated equine estrogen may remain active for several weeks after treatment has ended, due to storage in adipose

tissue (93). Many patients on a cyclic estrogen regimen may find that, for each cycle, it takes several days before hot flashes diminish, and by the end of the week in which no estrogen is taken, hot flashes have returned. For this and other reasons, the current trend is toward prescribing continuous daily estrogen.

The most commonly used regimen for treating hot flashes in the United States is 0.625 to 1.25 mg of oral conjugated equine estrogen (Premarin). Many other oral preparations are available in equivalent doses (see Chapter 6). Transdermal estradiol (Estraderm 0.05 to 0.10 mg/day) has been gaining popularity. Estrogen is also available as subcutaneous implants, injectables, and vaginal creams. Most are effective in treating hot flashes.

Oral estrogen has been in use for many years and has been the most extensively studied of the treatments for hot flashes. In a double-blind, placebo-controlled crossover study of conjugated equine estrogen (1.25 mg), Coope et al. (94) reported that after the first 3 months, hot flashes were reduced by about 90% in women on estrogen and by about 62% in women on placebo (Fig. 14). In another placebo-controlled trial, Campbell and Whitehead (95) sought to assess the efficacy of conjugated estrogen (1.25 mg) in relieving hot

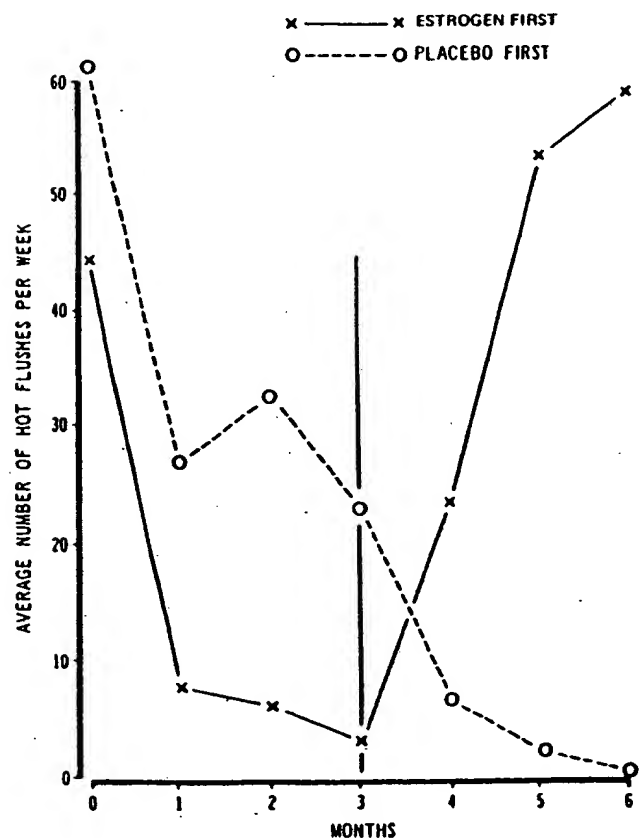


FIG. 14. Hot flush count during the 6-month trial. (From ref. 94, with permission.)

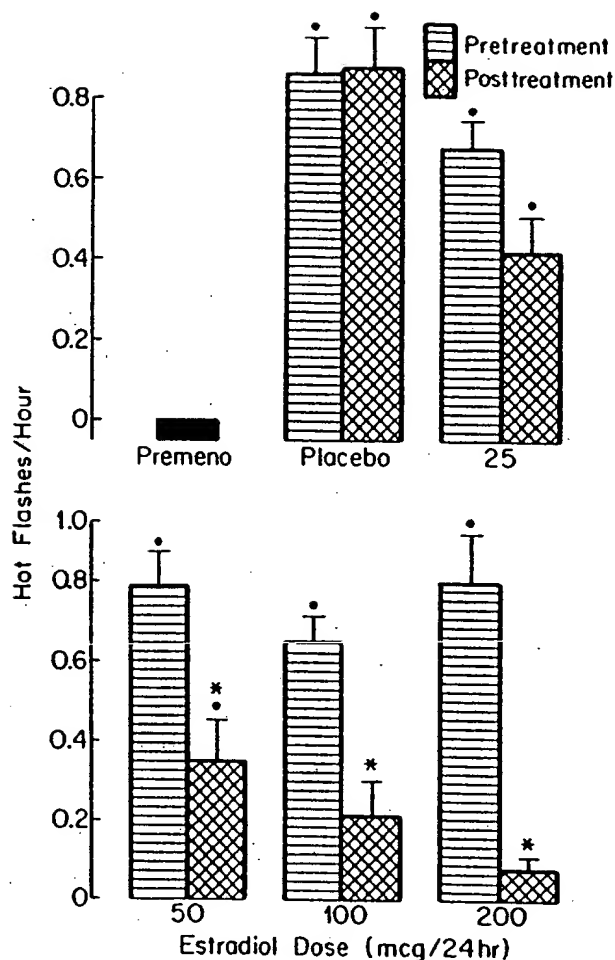


FIG. 15. Mean  $\pm$  SE rate of occurrence of hot flashes in the study groups and premenopausal women (Premeno) before and during transdermal  $E_2$  administration. (From ref. 96, with permission.)

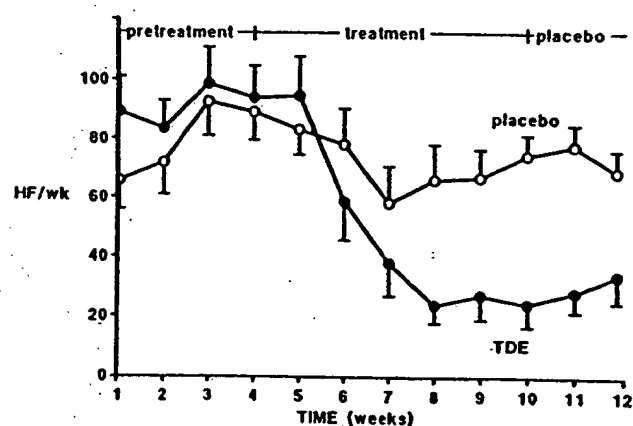


FIG. 16. Total subjective hot flashes (HF) recorded by patients on transdermal estradiol (TDE) patch ( $N = 10$ ) and placebo ( $N = 8$ , first seven weeks;  $N = 7$ , last five weeks) for each study week. (From ref. 97, with permission.)

flashes and other symptoms of menopause such as vaginal dryness, insomnia, anxiety, irritability, and memory loss. Estrogen was significantly better than placebo in improving all these symptoms. Hot flashes were improved by 40% to 50% with estrogen and by approximately 10% with placebo (as assessed by graphic rating scores). In this study, one group of subjects had symptoms such as insomnia, but they did not have hot flashes. Treatment with estrogen improved some of their symptoms, but not their insomnia. This is in contrast to the alleviation of the insomnia for those women who also complained of hot flashes. The investigators concluded that much of the insomnia of women with hot flashes is the result of nocturnal hot flashes.

Transdermal patches provide a continuous diffusion of estradiol and are effective in reducing hot flashes. A dose-response relationship between dose of transdermal estradiol (25, 50, 100, and 200  $\mu$ g/24 hr) and hot flash frequency, using subjective and objective criteria, was demonstrated in a double-blind study by Steingold (96) (Fig. 15). Hot flashes were significantly reduced at all doses of estradiol, with a progressive decline in hot flashes as estradiol increased; hot flashes were not appreciably reduced by placebo. The highest dose of 200  $\mu$ g/day resulted in a 91% reduction in the number of hot flashes.

Haas et al. (97) compared the effects of 6 weeks of transdermal estradiol (10  $cm^2$ , 50  $\mu$ g/day) with that of placebo, on subjectively and objectively measured hot flashes in a double-blind, placebo-controlled study. While changes in plasma estradiol and LH levels were measurable within 8 hr of the application of the patch, a decline in hot flashes occurred only gradually over the next 4 weeks. At that point there was a 74% decrease in subjectively reported hot flashes and an 85% decrease in objectively monitored hot flashes (Fig. 16). Women on placebo reported a 27% reduction in hot flashes (not statistically significant) during the first 3 weeks of the study.

Stanczyk (98) compared transdermal estradiol with subdermal estradiol. Hot flashes were eliminated in all patients, regardless of the mode of estrogen delivery.

In addition to ameliorating hot flashes, other complaints that may be improved by estrogen include insomnia (74,95), vaginal dryness (95), memory/concentration (95), lower urinary tract problems (95), and mood (95,99).

#### Nonestrogenic Treatments

Although most women find that estrogen relieves their hot flashes, there are some for whom estrogen is contraindicated or who find the side effects unacceptable, some whose hot flashes are not responsive to es-

trogen, even at elevated doses, and others who prefer not to remain on estrogen for a prolonged period of time.

### Progestins

Medroxyprogesterone acetate (MPA) is a nonestrogenic steroid. Several double-blind, placebo-controlled studies have shown that MPA decreases the number of hot flashes. Injected intramuscularly, a dose of 150 mg/month MPA resulted in a 90% reduction in hot flashes, compared with a 25% reduction in the placebo group (100). The major side effect was abnormal uterine bleeding (43%). Morrison et al. (101) conducted a study of MPA (50, 100, and 150 mg im) in which a dose-response relationship was shown, with about 75% improvement for those on 50 mg, and 90% to 100% relief for those on 150 mg by week four of treatment. Most women in the placebo group dropped out of the study. For those who remained, the placebo was ineffective. In this study, only two subjects on MPA (of 36 women) had abnormal bleeding.

Taken orally, MPA has fewer side effects. In a double-blind, placebo-controlled trial, MPA (20 mg/day) resulted in an approximately 74% decline in the number of reported hot flashes by the third month of treatment; placebo caused a reduction in hot flashes of about 26% (Fig. 17) (102). Albrecht et al. (103) measured hot flashes both subjectively and objectively in response to 20 mg/day, oral MPA. Reported hot flashes

decreased by 90% in women on MPA and by 25% in those on placebo. Finger skin temperature elevations and associated LH pulses, the objective indicators of hot flashes, were also reduced.

Another progestin, megestrol acetate (MA), has been tested and found to be effective in treating hot flashes. Oral MA significantly reduced hot flashes (no placebo control) whether measured subjectively or objectively, in a dose-response fashion with increasing doses of MA (20, 40, 80 mg/day) (Fig. 18). Few side effects were reported, and no abnormal bleeding or depression (124).

Sherwin and Gelfand (104) compared women on conjugated equine estradiol alone, with those on estradiol + medroxyprogesterone acetate (MPA). Both regimens resulted in a reduction in hot flashes. Estradiol was administered on days 1 to 25, and MPA on days 15 to 25, leaving days 26 to 30 hormone-free. For 3 weeks of each cycle hot flashes were diminished. During the fourth week, which was hormone-free, hot flash frequency increased.

### Clonidine

Clonidine, an  $\alpha$ -adrenergic receptor agonist that influences vascular responsiveness, has been used in the treatment of hot flashes. Clayden and colleagues (105) reported a double-blind, placebo-controlled crossover study of 86 women with hot flashes, and they demonstrated that clonidine (0.05 to 0.15 mg/day) reduced the

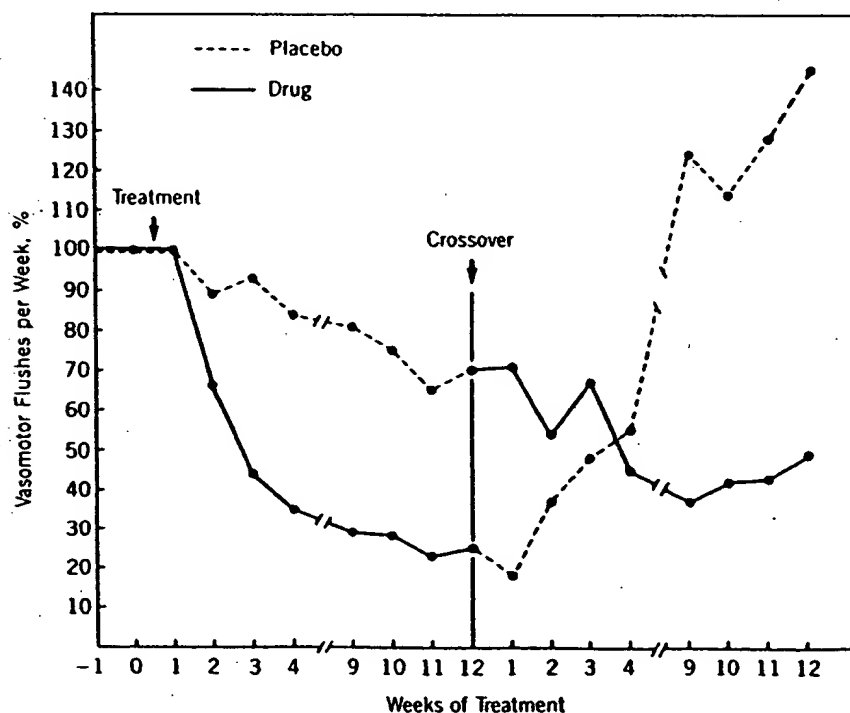


FIG. 17. Effect of oral medroxyprogesterone acetate on frequency of hot flashes. Mean number of vasomotor flashes as a percent change from pretreatment (week -1 to 0). (From ref. 102, with permission.)

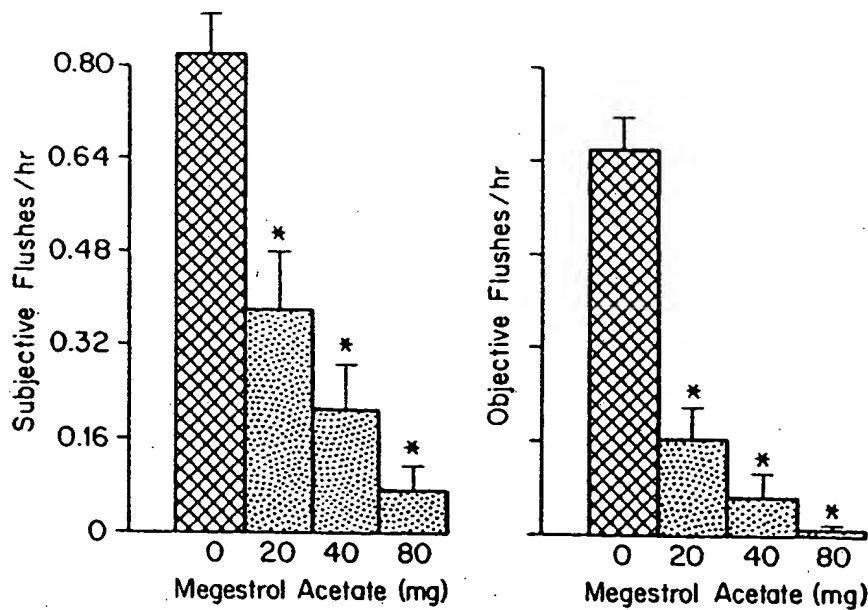


FIG. 18. The mean ( $\pm$  SE) subjective and objective flushes per hour before and following the oral administration of the various doses of megestrol acetate. \*Significantly different ( $p < 0.01$ ) from baseline. (From ref. 124, with permission.)

number and intensity of hot flashes. However, as in the studies of estrogen, women on placebo also reported a reduction in hot flashes almost equal to that of women on clonidine (Fig. 19). Dry mouth was the primary complaint of those on clonidine. Other side effects, including insomnia, headache, depression, and nausea, were reported both by those on clonidine and on placebo. In another study, Laufer and co-workers (106) demonstrated a dose-response relationship between clonidine (0.1, 0.2, 0.4 mg/day) and objectively recorded hot flashes in six women. At the highest dose, reduction in hot flashes was 46%; the reduction with placebo was small and not statistically significant.

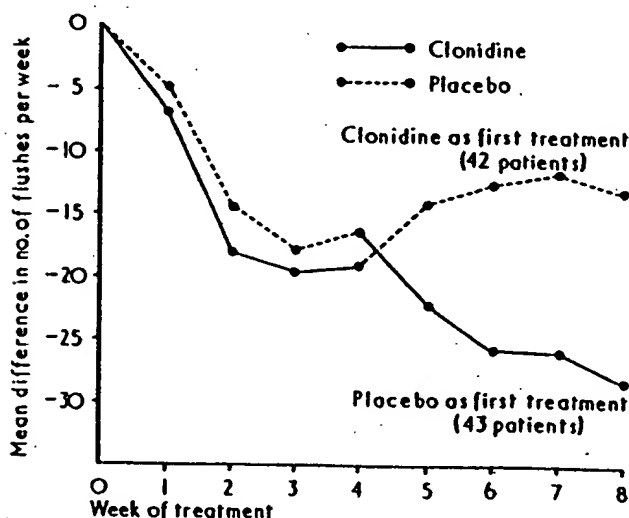


FIG. 19. Mean change in number of flushes from initial values. (From ref. 105, with permission.)

cant. Of the initial 10 subjects, four withdrew due to side effects, which included nausea, fatigue, headaches, dizziness, and dry mouth.

When clonidine was administered intravenously to menopausal women with hot flashes, Tulandi et al. (107) obtained somewhat different results. Subjects who received clonidine (0.075 mg in 10 ml physiological saline) did report significantly fewer hot flashes; however, objective recordings indicated a continuation of the pattern of episodic increases in finger skin temperature and the associated pulses of LH characteristic of hot flashes.

Ginsburg et al. (108) examined vascular responsiveness in menopausal women before and after oral clonidine treatment. They measured peripheral vasodilatory responses to infusion of the vasoactive substances norepinephrine, epinephrine, and angiotensin. Forearm and hand blood flow responses in the infusions were diminished after clonidine treatment. The investigators suggest that clonidine might reduce the peripheral vasodilation that accompanies a hot flash, and that given the reduced response to angiotensin, clonidine might be acting in some way other than through peripheral adrenergic mechanisms.

Lofexidine, another  $\alpha$ -agonist, and  $\alpha$ -methyl-dopa, whose primary metabolite,  $\alpha$ -methylnorepinephrine, is an  $\alpha$ -receptor agonist, have also demonstrated effectiveness in reducing hot flashes (109,110).

#### Propranolol

Propranolol, a peripherally and centrally acting beta-receptor blocking agent, has been studied with

mixed results. Erkkola and colleagues (111) reported that 60 mg/day of propranolol slightly reduced hot flashes. The reduction was from approximately 9.4 hot flashes/day to 7.8 hot flashes/day. There was no placebo control. Coope et al. (75), in a randomized double-blind placebo-controlled trial, found 40 mg of propranolol daily to be no more effective than placebo in reducing hot flashes. The slight reduction in hot flashes was similar to that reported by Erkkola. No side effects were seen among the women on propranolol. A statistically significant reduction in hot flash frequency was reported by Alcock et al. (112) in 70% of their subjects. However, there was no report of the extent of the reduction, so it is difficult to assess whether this had clinical significance. Side effects (including lightheadedness, nausea, and fatigue) occurred in 24% of those on propranolol (80 mg/day).

### **Bellergal**

Bellergal is a combination of belladonna alkaloids, ergotamine tartrate, and phenobarbital. In a double-blind, placebo-controlled study, Leberherz and French (113) found Bellergal to be significantly more effective than placebo in reducing subjectively reported hot flashes (60% decrease in hot flashes versus 22% decrease, respectively). The specific mechanism of action on hot flashes is unknown. Bellergal has sedative effects and is not a treatment of choice. One must also consider the varied actions of the three components and be aware of possible interactions with other drugs.

## **NONPHARMACOLOGIC APPROACHES**

The impetus to explore alternative therapies springs not from a pressing need for a more effective treatment, since estrogen is very effective, but primarily from a concern over the safety of estrogen treatment, and a need for alternatives for those for whom estrogen is contraindicated, who cannot tolerate estrogen, or who choose not to take estrogen. Unfortunately, the therapeutic efficacy of most alternatives has not been adequately tested.

### **Ambient Temperature**

As indicated earlier, the surrounding air temperature can have a significant impact on both the frequency and intensity of hot flashes. For women who have difficulty sleeping due to frequent hot flashes, maintaining a cool bedroom temperature is one way to ameliorate hot flashes and reduce nighttime awakenings. It is not as easy to control the temperature of one's envi-

ronment during the day, but if possible to achieve, a cool environment would reduce hot flashes.

### **Vitamin E**

In the 1940s a number of studies tested the effectiveness of vitamin E in treating hot flashes (114-116). Most of these investigations found vitamin E to have value in treating hot flashes. But the studies were neither double-blind nor placebo-controlled. In 1953, Blatt et al. (117) conducted a double-blind study comparing the effect of vitamin E, estrogen, and a placebo (no crossover) on a complex of menopausal symptoms (not hot flashes alone, but as part of a group of 11 symptoms). They found vitamin E to be no more effective than placebo, and considerably less effective than estrogen in treating this symptom complex. This study is often quoted as demonstrating the lack of effectiveness of vitamin E for treating hot flashes, a conclusion that cannot be drawn from the data. Some women report anecdotally that vitamin E is very effective in ameliorating their hot flashes (F. Kronenberg, *unpublished data*). A properly controlled study of vitamin E and hot flashes is warranted in order to determine the degree of effectiveness and for whom the treatment might be most effective.

## **BEHAVIORAL TREATMENTS**

Behavioral methods for moderating hot flashes have received limited study. Freedman and Woodward (81) compared paced respiration and muscle relaxation for their effects on objectively recorded hot flashes. Paced respiration training significantly reduced the frequency of hot flashes (by about 40%) as compared with progressive muscle relaxation training. A variety of behavioral modalities should be evaluated in rigorously designed studies.

### **Acupuncture**

Studies to evaluate the effectiveness of acupuncture in treating hot flashes are underway. Preliminary data from Hammar and colleagues (118) suggest that electrostimulated acupuncture decreases the frequency of hot flashes. Data are as yet insufficient to make possible conclusions or recommendations.

### **Exercise**

The effect of exercise on hot flashes is being investigated. Hammar et al. (119) found that women who belonged to a "gymnastic club" reported less severe

hot flashes than women who did not belong. They did not, however, investigate the physical activity of the latter group. Since exercise results in a great variety of physiological changes, a more rigorous study is needed to determine what component of exercise-induced responses might be responsible for the amelioration of hot flashes.

### Diet

Information on how specific foods affect hot flashes is anecdotal. Some women report that caffeine, alcohol, or spicy foods seem to trigger hot flashes. Eliminating foods suspected of aggravating hot flashes can be tried. No scientific data are available regarding either short-term trigger effects or longer-term effects of dietary patterns on hot flashes.

### CONCLUSION

We have gained considerable knowledge about hot flashes over the past two decades, although many questions remain unanswered and the specific genesis of hot flashes remains unknown. Even the role of estrogen in the etiology of hot flashes, or the mechanism by which estrogen relieves hot flashes, is still not understood.

While the patterns of hot flashes may be varied, there are commonalities in their physiology and subjective manifestations. Yet the significance of hot flashes to an individual woman's quality of life varies greatly. Currently in the United States there are about 40 million women of menopausal age. The majority of women will at some time experience hot flashes, and for most of these women, hot flashes will last 1 to 3 years and will not be particularly frequent or disruptive. However, 3 to 5 million women will have severe and frequent hot flashes that can be physically and psychologically debilitating. These are the women who most likely would seek medical assistance.

During a hot flash, elements of thermoregulatory, cardiovascular, and endocrine systems act in concert. These elements simultaneously serve other, nonthermal functions such as keeping blood flow and blood pressure regulated. It is an immense challenge to the researcher, given physiological complexity, to produce an explanation of hot flashes that integrates these various interacting physiological factors, as well as behavioral, psychophysiological, and even psychosocial components. Understanding the cause of hot flashes would provide insights into normal and abnormal changes at menopause. A more complete knowledge of the thermoregulatory, cardiovascular, and psychophysiology of women with hot flashes as compared to women without hot flashes may enable us to predict

who is most likely to be affected, and to identify additional approaches to the management and treatment of hot flashes.

As information increases about factors that are predictive of hot flashes, and about other health problems that can influence treatment choice, an individualized approach is increasingly indicated. One dose, regimen, or approach does not fit all women. This makes it all the more urgent to understand the underlying physiology, so we can broaden the treatment options available to women.

### REFERENCES

1. Molnar GW. Body temperatures during menopausal hot flashes. *J Appl Physiol* 1975;38:499-503.
2. Feldman JM, Postlethwaite RW, Glenn JF. Hot flashes and sweats in men with testicular insufficiency. *Arch Intern Med* 1976;136:606-608.
3. Steinfeld AD, Reinhardt C. Male climacteric after orchiectomy in patient with prostatic cancer. *Urology* 1980;16:620-622.
4. DeFazio J, Meldrum DR, Winer JH, Judd HL. Direct action of androgen on hot flushes in the human male. *Maturitas* 1984;6:3-8.
5. Frodin T, Alund G, Varenhorst E. Measurement of skin blood-flow and water evaporation as a means of objectively assessing hot flushes after orchidectomy in patients with prostatic cancer. *Prostate* 1985;7:203-208.
6. Linde R, Doelle GC, Alexander N, Kirchner F, Vale W, Rivier J, Rabin D. Reversible inhibition of testicular steroidogenesis and spermatogenesis by a potent gonadotropin-releasing hormone agonist in normal men. *N Engl J Med* 1981;305:663-667.
7. Garnick MB, Glode LM, Smith JA Jr, Max DT. Leuprolide: a review of its effects in comparison with diethylstilboestrol in the treatment of advanced cancer of the prostate. *Br J Clin Pract* 1985;39:73-76.
8. Newton M, Odom PL. The menopause and its symptoms. *South Med J* 1964;57:1309-1313.
9. Neugarten BL, Kraines RJ. "Menopausal symptoms" in women of various ages. *Psychosom Med* 1965;27:266-273.
10. Jaszmann L, Van Lith ND, Zaat JCA. The age at menopause in the Netherlands: the statistical analysis of a survey. *Med Gynaec Androl Sociol* 1969;4:256-262.
11. Rybo G, Westerberg H. Symptoms in the post-menopause—a population study. A preliminary report. *Acta Obstet Gynecol Scand* 1971;50:25.
12. Thompson B, Hart SA, Durno D. Menopausal age and symptomatology in a general practice. *J Biosoc Sci* 1973;5:71-82.
13. McKinlay SM, Jefferys M. The menopausal syndrome. *Br J Prev Soc Med* 1974;28:108-115.
14. Kronenberg F. Hot flashes: epidemiology and physiology. *Ann NY Acad Sci* 1990;592:52-86.
15. Sharma VK, Saxena MSL. Climacteric symptoms: a study in the Indian context. *Maturitas* 1981;3:11-20.
16. Moore B. Climacteric symptoms in an African community. *Maturitas* 1981;3:25-29.
17. Wright AL. On the calculation of climacteric symptoms. *Maturitas* 1981;3:55-63.
18. Lock M, Kaufert P, Gilbert P. Cultural construction of the menopausal syndrome: the Japanese case. *Maturitas* 1988;10:317-332.
19. Agoestina T, van Keep PA. The climacteric in Bandung, West Java province, Indonesia; a survey of 1025 women between 40-55 years of age. *Maturitas* 1984;6:327-333.
20. Kay M, Voda AM, Olivas G, Rios F, Imle M. Ethnography of the menopause-related hot flash. *Maturitas* 1982;4:217-227.

21. Beyene Y. Cultural significance and physiological manifestations of menopause a biocultural analysis. *Cult Med Psychiatry* 1986;10:47-71.
22. Sukwatana P, Meekhangvan J, Tamrongterakul T, Tanapat Y, Asavarait S, Boonjitrpimon P. Menopausal symptoms among Thai women in Bangkok. *Maturitas* 1991;13:217-228.
23. Jalbuena JR. Menopause among Filipino women. *Int Meno Congr* 1990;20:[abstract].
24. Liu CH. Medical care-seeking behaviour among climacteric women in Taiwan. *Int Meno Congr* 1980;18:[abstract].
25. Lock M. Ambiguities of aging: Japanese experience and perceptions of menopause. *Cult Med Psychiatry* 1986;10:23-46.
26. Feldman BM, Voda AM, Gronseth E. The prevalence of hot flash and associated variables among perimenopausal women. *Res Nurs Health* 1985;8:261-268.
27. Voda AM, Feldman BM, Gronseth E. Description of the hot flash: sensations, meaning and change in frequency across time. In: Nodelovitz M, van Keep P, eds. *The climacteric in perspective*. Lancaster, England: MTP Press; 1986:259-269.
28. Berg G, Gottvall T, Hammar M, Lindgren R. Climacteric symptoms among women aged 60-62 in Linköping, Sweden, in 1986. *Maturitas* 1988;10:193-199.
29. Voda AM. Climacteric hot flash. *Maturitas* 1981;3:73-90.
30. Gannon L, Hansel S, Goldwin J. Correlates of menopausal hot flashes. *J Behav Med* 1987;10:277-285.
31. Sherman BM, Wallace RB, Bean JA, Chang Y, Schlabaugh L. The relationship of menopausal hot flushes to medical and reproductive experience. *J Gerontol* 1981;36:306-309.
32. Erlik Y, Meldrum DR, Judd HL. Estrogen levels in postmenopausal women with hot flashes. *Obstet Gynecol* 1982;59:403-407.
33. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Am J Hum Biol* 1992;4:37-46.
34. Ginsburg J, Swinhoe J, O'Reilly B. Cardiovascular responses during the menopausal hot flush. *Br J Obstet Gynaecol* 1981;88:925-930.
35. Kronenberg F, Cote LJ, Linkie DM, Dyrenfurth I, Downey JA. Menopausal hot flashes: thermoregulatory, cardiovascular, and circulating catecholamine and LH changes. *Maturitas* 1984;6:31-43.
36. Tataryn IV, Lomax P, Bajorek JG, Chesarek W, Meldrum DR, Judd HL. Postmenopausal hot flushes: a disorder of thermoregulation. *Maturitas* 1980;2:101-107.
37. Sturdee DW, Wilson KA, Pipili E, Crocker AD. Physiological aspects of menopausal hot flash. *Br Med J* 1978;2:79-80.
38. Casper RJ, Yen SSC, Wilkes MM. Menopausal flushes: a neuroendocrine link with pulsatile luteinizing hormone secretion. *Science* 1979;205:823-825.
39. Tataryn IV, Meldrum DR, Lu KH, Frumar AM, Judd HL. LH, FSH and skin temperature during menopausal hot flush. *J Clin Endocrinol Metab* 1979;49:152-154.
40. Casper RF, Yen SSC. Neuroendocrine changes during menopausal flushes. In: Norman RL, ed. *Neuroendocrine aspects of reproduction*. New York: Academic Press; 1983:359-378.
41. Molnar GW. Investigation of hot flashes by ambulatory monitoring. *Am J Physiol* 1979;6:R306-R310.
42. Aksel S, Schomberg DW, Iyrey L, Hammond CB. Vasomotor symptoms, serum estrogens and gonadotropin levels in surgical menopause. *Am J Obstet Gynecol* 1976;12:165-169.
43. Hutton JD, Murray MAF, Jacobs HS, James VHT. Relation between plasma oestrone and oestradiol and climacteric symptoms. *Lancet* 1978; April:678-681.
44. Badawy SZA, Elliott LJ, Elbadawi A, Marshall LD. Plasma levels of oestrone and oestradiol-17B in postmenopausal women. *Br J Obstet Gynaecol* 1979;86:56-63.
45. Stone SC, Mickal A, Rye PH. Postmenopausal symptomatology, maturation index, and plasma estrogen levels. *Obstet Gynecol* 1975;45:625-627.
46. Meldrum DR, Tataryn IV, Frumar AM, Erlik Y, Lu KH, Judd HL. Gonadotropins, estrogens, and adrenal steroids during the menopausal hot flash. *J Clin Endocrinol Metab* 1980;50:685-689.
47. Hagen C, Christiansen C, Christensen MS, Transbol I. Climacteric symptoms, fat mass, and plasma concentrations of LH, FSH, Prl, oestradiol-17B and androstenedione in the early post-menopausal period. *Acta Endocrinol (Copenh)* 1982;101:87-92.
48. Mango D, Scirpa P, Battaglia F, Bini E. Plasma androstenedione and oestrone levels in the climacteric syndrome. *Maturitas* 1984;5:245-250.
49. Bider D, Ben-Rafael Z, Mashiach S, Serr DM, Blankstein J. Hot flushes during Gn-RH analogue administration despite normal serum oestradiol levels. *Maturitas* 1989;11:223-228.
50. Utian WH. The true clinical features of postmenopause and oophorectomy, and their response to oestrogen therapy. *S Afr Med J* 1972;46:732-737.
51. DeFazio J, Meldrum DR, Laufer L, Vale W, Rivier J, Lu JKH, Judd HL. Induction of hot flashes in premenopausal women treated with a long-acting GnRH agonist. *J Clin Endocrinol Metab* 1983;56:445-448.
52. Lemay A, Maheux R, Faure N, Jean C, Fazekas ATA. Reversible hyperestrogenism induced by repetitive LHRH agonist administration in the treatment of endometriosis. *17th Int Congr Endocrinol* 1984;1012.
53. Yen SSC. The biology of menopause. *J Reprod Med* 1977;18:287-296.
54. Silva NL, Boulant JA. Effects of testosterone, estradiol, and temperature on neurons in preoptic tissue slices. *Am J Physiol* 1986;250:R625-R632.
55. Israel SL, Schneller O. The thermogenic property of progesterone. *Fertil Steril* 1950;1:53-64.
56. Marrone BL, Gentry RT, Wade GN. Gonadal hormones and body temperature in rats: effects of estrous cycles, castration and steroid replacement. *Physiol Behav* 1976;17:419-425.
57. Altura BM. Sex as a factor influencing the responsiveness of arterioles to catecholamines. *Eur J Pharmacol* 1972;20:261-265.
58. Ginsburg J, Hardiman P, O'Reilly B. Peripheral blood flow in menopausal women who have hot flushes and in those who do not. *Br Med J* 1989;298:1488-1490.
59. Campbell S. Double-blind psychometric studies on the effects of natural estrogens on post menopausal women. In: Campbell S, ed. *The management of the menopausal and post menopausal years*. Baltimore: University Park Press; 1976:149-158.
60. Bohler CS-S, Greenblatt RB. The pathophysiology of the hot flash. In: Greenblatt RB, Mahesh VB, McDonough PG, eds. *The menopausal syndrome*. New York: Medcom Press; 1974:29-37.
61. Mulley G, Mitchell JRA, Tattersall RB. Hot flushes after hypophysectomy. *Br Med J* 1977;2:1062.
62. Meldrum DR, Erlik Y, Lu JKH, Judd HL. Objectively recorded hot flushes in patients with pituitary insufficiency. *J Clin Endocrinol Metab* 1981;52:684-687.
63. Casper RF, Yen SSC. Menopausal flushes: effect of pituitary gonadotropin desensitization by a potent luteinizing hormone releasing factor agonist. *J Clin Endocrinol Metab* 1981;53:1056-1058.
64. Lightman SL, Jacobs SJ, Maguire AK. Down regulation of gonadotropin secretion in postmenopausal women by superactive LHRH analogue: lack of effect on menopausal flushing. *Br J Obstet Gynaecol* 1982;89:977-980.
65. Ravnkar V, Elkind-Hirsch K, Schiff I, Ryan KJ, Tulchinsky D. Vasomotor flushes and the release of peripheral immunoreactive luteinizing hormone-releasing hormone in postmenopausal women. *Fertil Steril* 1984;41:881-887.
66. Gambone J, Meldrum DR, Laufer L, Chang RJ, Lu JKH, Judd HL. Further delineation of hypothalamic dysfunction responsible for menopausal hot flashes. *J Clin Endocrinol Metab* 1984;59:1097-1102.
67. Whitby G, Axelrod J, Weil-Malherbe H. The fate of [H]nor-epinephrine in animals. *J Pharmacol Exp Ther* 1961;132:192-201.
68. Mashchak CA, Kletzky OA, Artal R, Mishell DR Jr. The relation of physiological changes to subjective symptoms in postmenopausal women with and without hot flushes. *Maturitas* 1984;6:301-308.
69. Genazzani AR, Petraglia F, Facchinetti F, Facchini V, Volpe A, Alessandrini G. Increase of proopiomelanocortin-related



- peptides during subjective menopausal flushes. *Am J Obstet Gynecol* 1984;149:775-779.
70. Meldrum DR, DeFazio JD, Erlik Y, Lu JKH, Wolfsen AF, Carlson HE, Hershman JM, Judd HL. Pituitary hormones during the menopausal hot flash. *Obstet Gynecol* 1984;64:752-756.
  71. Erlik Y, Tataryn IV, Meldrum DR, Lomax P, Bajorek JG, Judd HL. Association of waking episodes with menopausal hot flushes. *JAMA* 1981;245:1741-1744.
  72. Shaver J, Giblin E, Lentz M, Lee K. Sleep patterns and stability in perimenopausal women. *Sleep* 1988;11:556-561.
  73. Thomson J, Oswald I. Effect of oestrogen on the sleep, mood, and anxiety of menopausal women. *Br Med J* 1977;2:1317-1319.
  74. Schiff I, Regestein Q, Tulchinsky D, Ryan KJ. Effects of estrogens on sleep and psychological state of hypogonadal women. *JAMA* 1979;242:2405-2407.
  75. Coope J, Williams S, Patterson JS. A study of the effectiveness of propranolol in menopausal hot flushes. *Br J Obstet Gynaecol* 1978;85:472-475.
  76. Molnar GW. Menopausal hot flashes: their cycles and relation to air temperature. *Obstet Gynecol* 1980;57:52S-55S.
  77. Kronenberg F, Barnard RM. Modulation of menopausal hot flashes by ambient temperature. *J Therm Biol* 1992;17:43-49.
  78. Casper RF, Yen SSC. Neuroendocrinology of menopausal flushes: an hypothesis of fluid mechanism. *Clin Endocrinol* 1985;22:293-312.
  79. Rebar RW, Spitzer IB. The physiology and measurement of hot flushes. *Am J Obstet Gynecol* 1987;156:1284-1288.
  80. Zichella L, Tesseri E, Falaschi P, Gambacciani M, Cagnacci A, Strigini F, Melis GB, Fioretti P. Psychoneuroendocrinology of postmenopausal hot flushes. In: Pancheri P, Zichella L, eds. *Biorhythms and stress in the pathophysiology of reproduction*. New York: Hemisphere Publishing; 1988:549-565.
  81. Freedman RR, Woodward S. Behavioral treatment of menopausal hot flushes: evaluation by ambulatory monitoring. *Am J Obstet Gynecol* 1992;167:436-439.
  82. Judd HL. Pathophysiology of menopausal hot flushes. In: Meites J, ed. *Neuroendocrinology of aging*. New York: Plenum Press; 1983:173-202.
  83. Tulandi T, Lal S. Menopausal hot flush. *Obstet Gynecol Surv* 1985;40:553-563.
  84. Ginsburg J, Hardiman P. What do we know about the pathogenesis of the menopausal hot flush? In: Sitruk-ware R, Utian WH, eds. *The menopause: a hormonal replacement therapy*. New York: Marcel Dekker; 1991:15-46.
  85. Kronenberg F, Downey JA. Thermoregulatory physiology of menopausal hot flushes: a review. *Can J Physiol Pharmacol* 1987;65:1312-1324.
  86. Kluger MJ. Fever: role of pyrogens and cryogens. *Physiol Rev* 1991;71:93-127.
  87. Lipton JM, Glyn JR. Central administration of peptides alters thermoregulation in the rabbit. *Peptides* 1980;1:15-18.
  88. Lipton JM, Glyn JR, Zimmer JA. ACTH and alpha-melanotropin in central temperature control. *Fed Proc* 1981;40:2760-2764.
  89. Murphy MT, Lipton JM.  $\beta$ -Endorphin: effect on thermoregulation in aged monkeys. *Neurobiol Aging* 1983;4:187-190.
  90. Reid RL, Hoff JD, Yen SSC, Li CH. Effect of exogenous  $\beta$ -endorphin on pituitary hormone secretion and its disappearance rate in normal human subjects. *J Clin Endocrinol Metab* 1981;52:1179-1183.
  91. Ferin M, Wehrenberg WB, Lam NY, Alston EF, Vande Wiele RL. Effect and site of action of morphine on gonadotropin secretion in the female rhesus monkey. *Endocrinology* 1982;111:1652-1656.
  92. Wehrenberg WB, Wardlaw SL, Frantz AG, Ferin M.  $\beta$ -Endorphin in hypophyseal portal blood: variations throughout the menstrual cycle. *Endocrinology* 1982;111:879-881.
  93. Barnes RB, Lobo RA. Pharmacology of estrogens. In: Mishell DR, ed. *Menopause: physiology and pharmacology*. Chicago: Year Book Medical Publishers; 1987:301-315.
  94. Coope J, Thomson JM, Poller L. Effects of "natural oestrogen" replacement therapy on menopausal symptoms and blood clotting. *Br Med J* 1975;4:139-143.
  95. Campbell S, Whitehead M. Oestrogen therapy and the menopausal syndrome. *Clin Obstet Gynaecol* 1977;4:31-47.
  96. Steingold KA. Treatment of hot flashes with transdermal estradiol administration. *J Clin Endocrinol Metab* 1985;61:627-632.
  97. Haas S, Walsh B, Evans S, Krache M, Ravnika V, Schiff I. The effect of transdermal estradiol on hormone and metabolic dynamics over a six-week period. *Obstet Gynecol* 1988;71:671-676.
  98. Stanczyk FZ. A randomized comparison of nonoral estradiol delivery in postmenopausal women. *Am J Obstet Gynecol* 1988;159:1540-1546.
  99. Dittkoff EC, Crary WG, Cristo M, Lobo R. Estrogen improves psychological function in asymptomatic postmenopausal women. *Obstet Gynecol* 1991;78:991-995.
  100. Bullock JL, Massey FM, Gambrell RD Jr. Use of medroxyprogesterone acetate to prevent menopausal symptoms. *Obstet Gynecol* 1975;46:165-168.
  101. Morrison JC, Martin DC, Blair RA, Anderson GD, Kincheloe BW, Bates GW, Hendrix JW, Rivlin ME, Forman EK, Propst MG, Needham R. The use of medroxyprogesterone acetate for relief of climacteric symptoms. *Am J Obstet Gynecol* 1980;138:99-104.
  102. Schiff I, Tulchinsky D, Cramer D, Ryan KJ. Oral medroxyprogesterone in the treatment of postmenopausal symptoms. *JAMA* 1980;244:1443-1445.
  103. Albrecht BH, Schiff I, Tulchinsky D, Ryan KJ. Objective evidence that placebo and oral medroxyprogesterone acetate therapy diminish menopausal vasomotor flushes. *Am J Obstet Gynecol* 1981;139:631-635.
  104. Sherwin BB, Gelfand MM. A prospective one-year study of estrogen and progestin in postmenopausal women: effects on clinical symptoms and lipoprotein lipids. *Obstet Gynecol* 1989;73:759-766.
  105. Clayden JR, Bell JW, Pollard P. Menopausal flushing: double-blind trial of a non-hormonal medication. *Br Med J* 1974;1:409-412.
  106. Laufer LR, Erlik Y, Meldrum DR, Judd HL. Effect of clonidine on hot flashes in postmenopausal women. *Obstet Gynecol* 1982;60:553-558.
  107. Tulandi T, Lal S, Kinch RA. Effect of intravenous clonidine on menopausal flushing and luteinizing hormone secretion. *Br J Obstet Gynaecol* 1983;90:854-857.
  108. Ginsburg J, O'Reilly B, Swinhoe J. Effect of oral clonidine on human cardiovascular responsiveness: a possible explanation of the therapeutic action of the drug in menopausal flushing and migraine. *Br J Obstet Gynaecol* 1985;92:1169-1175.
  109. Jones KP, Ravnika V, Schiff I. A preliminary evaluation of the effect of lofexidine on vasomotor flushes in postmenopausal women. *Maturitas* 1985;7:135-139.
  110. Nesheim B-I, Saetre T. Reduction of menopausal hot flushes by methyl dopa: a double blind crossover trial. *Eur J Clin Pharmacol* 1981;20:413-416.
  111. Erkkola R, Iisalo E, Punnonen R. The effect of propranolol and oxazepam on some vegetative menopausal symptoms. *Ann Clin Res* 1973;5:208-213.
  112. Alcock JM, Campbell D, Tribble D, Oldfield B, Cruess D. Double-blind, placebo-controlled, crossover trial of propranolol as treatment for menopausal vasomotor symptoms. *Clin Ther* 1981;3:356-364.
  113. Leberherz TB, French L. Nonhormonal treatment of the menopausal syndrome. *Obstet Gynecol* 1969;33:795-799.
  114. Christy CJ. Vitamin E in menopause. *Am J Obstet Gynecol* 1945;50:84-87.
  115. Ferguson HE. The use of vitamin E in menopausal syndrome. *VA Med Month* 1948;75:447-448.
  116. McLaren HC. Vitamin E in the menopause. *Br Med J* 1949;2:1378-1382.
  117. Blatt MHG, Weisbader H, Kupperman HS. Vitamin E and climacteric syndrome. *Arch Intern Med* 1953;91:792-796.



118. Hammar M, Lindgren R, Wyon Y, Lundeberg T. Does acupuncture influence the frequency of postmenopausal hot flushes? *NAMS* 1991;76:[abstract].
119. Hammar M, Berg G, Lindgren R. Does physical exercise influence the frequency of postmenopausal hot flushes? *Acta Obstet Gynecol Scand* 1990;69:409-412.
120. Lightman SL, Jacobs HS, Maguire AK, McGarrick G, Jeffcoate SL. Climacteric flushing: clinical and endocrine response to infusion of naloxone. *Br J Obstet Gynaecol* 1981;88:919-924.
121. Cignarelli M, Cicinelli E, Corso M, Cospite MR, Garutti G, Tafaro E, Giorgino R, Schonauer S. Biophysical and endocrine-metabolic changes during menopausal hot flashes: increase in plasma-free fatty acid and norepinephrine levels. *Gynecol Obstet Invest* 1989;27:34-37.
122. Tulandi T, Murphy BEP, Lal S. Plasma cortisol concentrations in women with menopausal flushes. *Maturitas* 1985;7:367-372.
123. Kronenberg F, Carraway RE. Changes in neurotensin-like immunoreactivity during menopausal hot flashes. *J Clin Endocrinol Metab* 1985;60:1081-1086.
124. Erlik Y, Meldrum DR, Lagasse LD, Judd HL. Effect of megesterol acetate on flushing and bone metabolism in postmenopausal women. *Maturitas* 1981;3:167-172.



# Prescription Drug Trends

a chartbook

July 2000

# **Prescription Drug Trends**

**a chartbook**

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July 2000

**Top 20 Prescription Drugs Ranked by Number of Dispensed Prescriptions, 1998**

exhibit

3.16

Rank	Product	Indication	1998 Prescriptions Dispensed (Million)	Brand or Generic?	Year First Marketed
1	Premarin (Wyeth-Ayerst)	hormone replacement	46.8	B/G	1964
2	Synthroid (Knoll)	thyroid replacement	38.8	B/G	1963
3	Hydrocodone w/APAP (Watson)	narcotic analgesic	29.4	G	1977
4	Trimox (Apothecon)	antibiotic	28.5	G	1977
5	Prilosec (Astra-Merck)	anti-ulcerant (proton pump inhibitor - PPI)	26.7	B	1989
6	Albuterol (Warrick)	bronchodilator	26.0	G	1982
7	Lipitor (Parke-Davis/Warner Lambert)	cholesterol-lowering	24.9	B	1997
8	Prozac (Dista/Lilly)	SSRI anti-depressant	24.8	B	1987
9	Lanoxin (Allen & Hansbury)	cardiotonic (for heart failure)	24.2	B/G	1967
10	Norvasc (Pfizer)	calcium channel blocker (for hypertension)	23.4	B	1992
11	Claritin (Schering)	antihistamine	22.3	B	1993
12	Zoloft (Roerig/Pfizer)	SSRI anti-depressant	21.0	B	1992
13	Paxil (SmithKline Beecham)	SSRI anti-depressant	19.0	B	1993
14	Vasotec (Merck)	calcium channel blocker (for hypertension)	18.5	B	1986
15	Zocor (Merck)	cholesterol-lowering	18.5	B	1992
16	Prempro (Wyeth-Ayerst)	hormone replacement	18.3	B	1995
17	Coumadin Sodium (DuPont)	anti-coagulant	17.9	B/G	1954
18	Zestril (Zeneca)	ACE inhibitor (for hypertension)	17.5	B	1988
19	Glucophage (Bristol-Myers Squibb)	anti-diabetic agent	17.2	B	1995
20	Augmentin (SmithKline Beecham)	antibiotic	15.7	B/G	1984

## notes

B = Brand name (has remaining patent life; no generic versions available).

B/G = Brand name product but generics available.

G = Generic.

Rankings and number of prescriptions represent total prescriptions dispensed through independent, chain, foodstore, long-term care, and mail order pharmacies.

## sources

Sonderregger Research Center analysis, based on:

Prescriptions Dispensed from IMS Health, Inc., *National Prescription Audit (NPA) Plus*, published in *Medical Marketing & Media*, May 1999.Year First Marketed from Top 200 listing published in *Pharmacy Times*, April 1999.

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